INTRA OPERATIVE HEMODYNAMIC STABILITY WITH ESMOLOL VERSUS CLONIDINE FOR LAPROSCOPIC APPENDICECTOMY

A STUDY OF 90 CASES

DISSERTATION SUBMITTED FOR THE DEGREE OF

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LIST OF ABBREVIATIONS USED

5HT3 5 - Hydroxy Tryptamine

ASA - American societies of Anesthesiologists

CBF - Cerebral blood flow

CMRO2 - Cerebral metabolic rate for oxygen

CNS - Central nervous system

CSF - Cerebrospinal fluid

GABA - Gamma amino butyric acid

GI - Gastrointestinal

ICP - Intra cranial pressure

IM - Intramuscular

IV - Intravenous

PONV - Post operative nausea vomiting

SVR - Systemic vascular resistance.

IAP - intra abdominal pressure

ABSTRACT

Background and objectives: Laparoscopic appendicectomy is associated with an appreciably high rate of intra operative haemodynamic instability associated with pneumoperitonium. This study is designed to compare the effectiveness of Esmolol and Clonidine for maintenance of intra operative hemodynamic stability in laproscopic appendicectomy.

Methods: In a randomized, double blind study, 30 patients of both sexes received Esmolol 0.5 mg/kg bolus before induction followed by infusion of 100μ/kg/min and 30 patients received infusion of Clonidine 3μ/kg in 100 ml normal saline 15 min before induction and 30 patients received a placebo of 100 ml normal saline before induction. Peri operative anaesthetic care was standardized in all patients. Patients were then observed for intra operative pulse rate, blood pressure.

Results: Esmolol and clonidine groups were found to have significantly lower heart rate and blood pressure during the intra operative period as compared to control group.

Conclusion: Both Esmolol and Clonidine produces hemodynamic stability for laproscopic appendicectomy, with more reduction in heart rate and blood pressure with Esmolol than Clonidine.

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INTRODUCTION

Laparoscopic surgeries have revolutionized surgeries and it has now become the “gold standard” of many surgical procedures, and has been promoted, as a “gentle surgery”. However, this procedure is not risk free. In fact it produces significant haemodynamic changes specially in elderly and haemodynamically compromised patients.

Pneumoperitoneum(Pnp) affects several homeostatic systems leading to alteration in acid-base balance, cardiovascular, pulmonary physiology and stress response. The extent of cardiovascular changes associated with pneumoperitoneum include an increase in mean arterial pressure decrease in cardiac output and increase in systemic vascular resistance which in turn compromise tissue perfusion.

Various pharmacological agents were chosen to prevent haemodynamic changes associated with pneumoperitoneum. Nitroglycerine was used to correct the reduction of cardiac output associated with increased pulmonary occlusion pressure and systemic vascular resistance.

Esmolol, an ultra short-acting cardio-selective ß1-receptor antagonist, has been shown to blunt haemodynamic responses to perioperative noxious stimuli.

Clonidine inhibits the release of catecholamine and vasopressin and thus modulates the haemodynamic changes induced by pneumoperitoneum.

Considering all these observations, the present study was designed to evaluate the type and extent of haemodynamic changes associated with laparoscopic surgery and also to find out the efficacy of clonidine and Esmolol in prevention of such haemodynamic changes.

AIM AND OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVE

To compare the effectiveness of Esmolol and clonidine for maintaining hemodynamic stability in laproscopic appendicetomy

SECONDARY OBJECTIVES

• To determine any adverse effects in the postoperative period.

• To determine the postoperative nausea and vomiting , analgesic requirement and sedation in each group

LAPAROSCOPIC APPENDICECTOMY

Laparoscopic surgeries are done very commonly nowadays in every parts of the world. They have many advantages compared to an open procedure like less surgical trauma, less intraoperative and postoperative pain, early discharge, and above all the cosmetic benefit. It requires the creation of a pneumoperitonium. CO2 is used for gas insufflation via a VERESS needle, at a rate of 1-6 litre /minute, to a pressure of 14-20mmhg. Intraoperative problems during laparoscopic surgery can be cardiovascular, respiratory, gastrointestinal, renal or metabolic related. Hemodynamic changes, decrease in venous return, reflux tachycardia and arrhythmias due to gas insufflation are the main cardiovascular problems. Respiratory problems are mainly due to pneumoperitonium, which may cause cephalad displacement of diaphragm. This leads to reduction in lung volumes including tidal volume, functional residual capacity, decreased pulmonary compliance, increased airway resistance, and also the risk of barotrauma during IPPV. Restriction in diaphragmatic mobility promotes uneven distribution of ventilation to the nondependent part of the lung, which can lead to ventilation- perfusion mismatch with hypoxemia and hypercarbia. (CO2 absorption from pneumoperitonium may also cause hypercarbia). For this reason ETCO2 (End tidal CO2) monitoring is very much desirable during

laparoscopic surgeries. Increased intra abdominal pressure may predispose to regurgitation and aspiration in those who are susceptible.

Gastrointestinal considerations during laparoscopic appendicectomy are mainly regarding injuries to the visceral organs that can be caused by the laparoscopic instruments. Trochar insertion can damage viscera; particularly a stomach distended by hand ventilation. There is increased incidence of nausea and vomiting after laparoscopic appendicectomy. (Incidence of up to 70% has been reported in some studies). Though the exact cause for this is not known residual pneumoperitonium is considered the main etiology. Intra-abdominal pressure >20mmhg adversely affects renal function and urine output. Renal blood flow and glomerular filtration rate decrease because of increase in renal vascular resistance, reduction in glomerular filtration gradient and decrease in cardiac output. Complications of gas insufflation can be arrhythmias, subcutaneous emphysema, pneumomediastinum, pneumopericardium, pneumothorax and venous gas embolism. In the preanaesthetic checkup, cardiac and respiratory function is assessed carefully. General anaesthesia with muscle paralysis intubation and IPPV is the most common method. If appropriate, general anaesthesia with spontaneous ventilation by using laryngeal mask airway can also be considered for ASA 1 or 2 patients with no other contraindications. Ventilatory pattern is adjusted according to respiratory and hemodynamic response of the patient. Large tidal volumes (12-15ml/kg) prevent progressive microatelectasis and hypoxemia and allows for more effective alveolar

ventilation and CO2 elimination. However peak airway pressure is monitored to check excessive increase. Nitrous oxide does not adversely affect surgical conditions during laparoscopic appendicectomy by causing bowel distension and does not increase the incidence of PONV. Isoflurane is the volatile anaesthetic of choice because it is less arrhythmogenic and cause less myocardial depression. Postoperative recovery is usually very rapid. PONV can be particularly troublesome after laparoscopic appendicectomy. Pain consists of an early transient vague abdominal and shoulder discomfort. Pain from trochar-puncture wounds are usually mild. Use of opioids should be accompanied by an antiemetic. Pulmonary function is better preserved following laparoscopic appendicectomy than in open appendicectomy.

Hemodynamic Problems During Laparoscopy

Hemodynamic changes observed during laparoscopy result from the combined effects of pneumoperitoneum, patient position, anaesthesia, and hypercapnia from the absorbed CO_2. In addition to these pathophysiologic changes, reflex increases of vagal tone and arrhythmias can also develop.

Peritoneal insufflation to IAPs higher than 10 mm Hg induces significant alterations of hemodynamics. These disturbances are characterized by decreases in cardiac output, increased arterial pressures, and elevation of systemic and pulmonary vascular resistances. Heart rates remain unchanged or increased only slightly. The decrease in cardiac output is proportional to the increase in IAP.

Cardiac outputs, which decrease shortly after the beginning of the peritoneal insufflation, subsequently increase, probably as a result of surgical stress.

The mechanism of the decrease of cardiac output is multifactorial. A decrease in venous return is observed after a transient increase in venous return at low IAPs (<10 mm Hg). Increased IAP results in caval compression, pooling of blood in the legs, and an increase in venous resistance. The decline in venous return, which parallels the decrease in cardiac output, is confirmed by a reduction in left ventricular end-diastolic volume measured using transesophageal echocardiography. Cardiac filling pressures, however, rise during peritoneal insufflation. The paradoxical increase of these pressures can be explained by the

increased intrathoracic pressure associated with pneumoperitoneum. Right atrial pressure and pulmonary artery occlusion pressure can no longer be considered reliable indices of cardiac filling pressures during pneumoperitoneum. The fact that atrial natriuretic peptide concentrations remain low despite increased pulmonary capillary occlusion pressure during pneumoperitoneum further suggests that abdominal insufflation interferes with venous return. The reduction in venous return and cardiac output can be attenuated by increasing circulating volume before the pneumoperitoneum is produced. Increased filling pressures can be achieved by fluid loading or tilting the patient to a slight head-down position before peritoneal insufflation, by preventing the pooling of blood with intermittent sequential pneumatic compression device, or by wrapping the legs with elastic bandages.

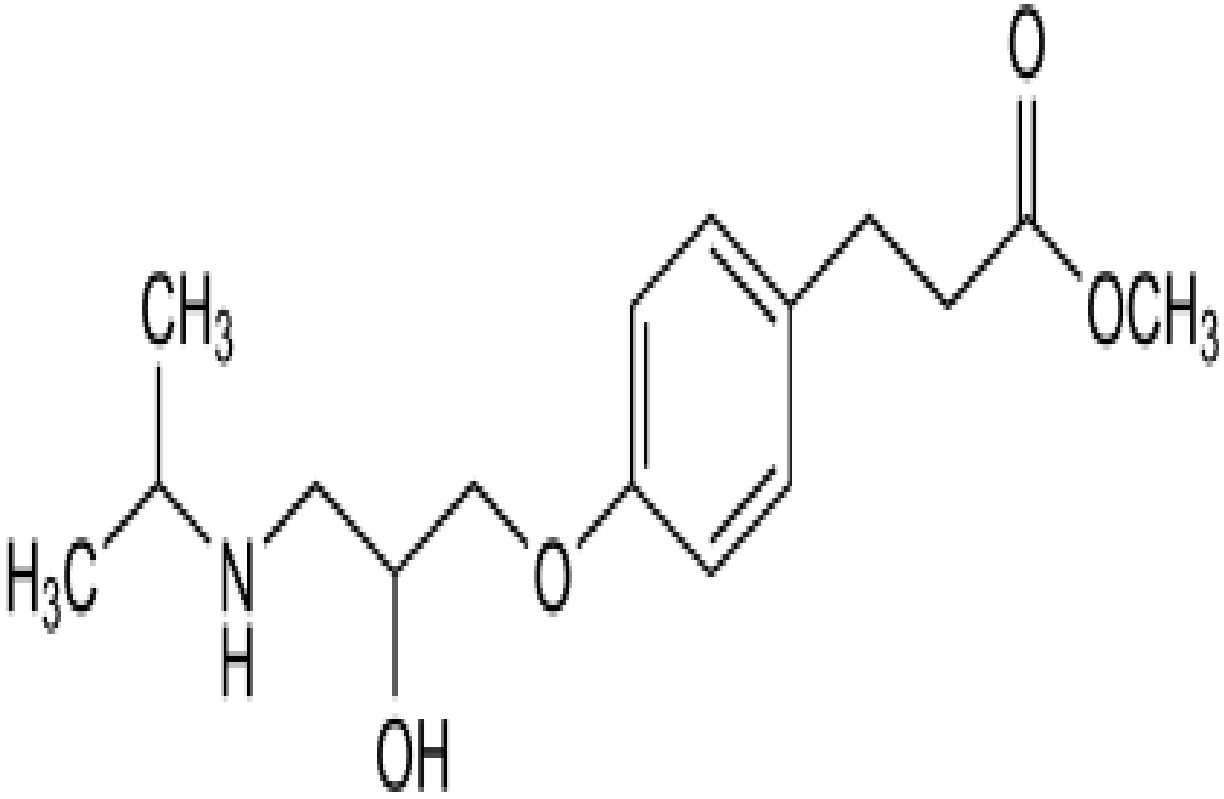
The ejection fraction of the left ventricle, assessed by echocardiography, does not appear to decrease significantly when IAP increases to 15 mm Hg. However, all studies describe an increase in systemic vascular resistance during the existence of the pneumoperitoneum. This increase in afterload is not a reflex sympathetic response to the decreased cardiac output. Systemic vascular resistance was reported to be increased in studies where no decrease in cardiac output was found. Although the normal heart tolerates increases in afterload under physiologic conditions, the increases in afterload produced by the

presence of a pneumoperitoneum can be deleterious to patients with cardiac disease.

The increase in systemic vascular resistance is affected by patient position. The trendelenburg position attenuates this increase; the head-up position aggravates it. The increase in systemic vascular resistance can be corrected by the administration of vasodilating anesthetic agents, such as isoflurane or direct vasodilating drugs, such as nitroglycerin or nicardipine.

The increase in systemic vascular resistance is thought to be mediated by mechanical and neurohumoral factors. The return of hemodynamic parameters to baseline values is gradual, taking several minutes, suggesting the involvement of neurohumoral factor(s). Catecholamines, the renin-angiotensin system, and especially vasopressin are all released during the presence of the pneumoperitoneum and may contribute to increasing the afterload. However, only the time course of vasopressin release parallels that of the increase in systemic vascular resistance. Increases in plasma vasopressin concentrations correlate with changes in intrathoracic pressure and transmural right atrial pressure. Mechanical stimulation of peritoneal receptors also results in increased vasopressin release, systemic vascular resistance, and arterial pressure. However, whether increasing IAP to 14 mm Hg is sufficient to stimulate these receptors is unknown. The increase in systemic vascular resistance also explains why the arterial pressure increases but the cardiac

output falls. Use of α_2-adrenergic agonists such as clonidine or dexmedetomidine and of β-blocking agents significantly reduces hemodynamic changes and anaesthetic requirements. Use of high doses of remifentanil almost completely prevents the hemodynamic changes.



ESMOLOL

PHARMACOLOGY OF ESMOLOL

In 1982 ZAROSLINSKI described the concept of an utra short acting β-adrenergic blocker. From this work esmolol which is a cardioselective β-blocker that has an extremely short duration of action was subsequently identified and characterised.

Chemistry

Esmolol (ASL – 8052) is chemically methyl 3- [4-(2-hydroxy-3-(isopropylamino)propoxy] phenyl propionate HCl, a molecular structure characteristic of second generation B-blockers. Esmolol contains an ester in the para position of phenyl ring. The presence and location of the ester is of fundamental importance in the determination of Esmolol`s cardioselectivity as well as its ultra short action.

Esmolol has the empirical formula $C_{16}H_{26}NO_4C_1$ and a molecular weight of 331.8 . It has one asymmetric centre and exists as an enentiomeric pair.

Esmolol hydrochloride is a white to off white crystalline powder. IT is a relatively hydrophilic compound which is very soluble in H_2O and freely soluble in alcohol.

Clinical pharmacology

Esmolol hydrochloride is a β_1-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action and no

significant intrinsic sympathomimetic or membrane stabilising activity at therapeutic dose. It inhibits the β_1 receptors located chiefly in cardiac muscles, but their preferential effect is not absolute and at higher doses it begins to inhibit β_2 receptors located chiefly in the bronchial and vascular musculature. Esmolol is 43 fold more potent at β-receptors in the atria (β_1) than in trachea (β_2). Blockade of vascular β-receptors required a dose several fold greater than that required for cardiac β – blockade. Esmolol does not have any effect on peripheral vascular resistance.

Pharmacokinetics and Metabolism

Esmolol is rapidly metabolised by hydrolysis of ester linkage, chiefly by esterase in the cytosol of red blood cells and not by plasma cholineesterases or red cell membrane acetylcholinesterase. Total body clearance in man was found to be 20 L/kg/hr which is greater than cardiac output. Thus the metabolism of Esmolol is not limited by the rate of blood flow to the metabolising tissues such as the liver and kidney. It has a rapid distribution half-life of about 2 minutes and an elimination half life of about 9 minutes.

After an appropriate loading dose, a steady state blood level of Esmolol are obtained within 5 minutes. Steady state is obtained within 30 minutes, without the loading dose. Steady state blood levels are maintained during infusion (20 min). Since it has a short half life, blood levels can be rapidly altered by increasing or decreasing the infusion rate.

Metabolism of Esmolol results in formation of an acidic metabolite (ALS-8123) phenyl propionic acid and methanol. The acidic metabolite has $1/1500^{th}$ the activity of Esmolol and its blood levels do not correspond to the level of β blockade. Acid metabolite has an elimination half life of about 3.7 hrs and is excreted in urine with a clearance approximately equal to the glomerular filtration rate. Elimination of acid metabolite is significantly decreased in patients with renal disease with the elimination half life increased to tenfold that of normal. Esmolol is unaffected by plasma cholinesterase. For full enzymatic activity, the Esmolol esterase in RBC cytosol requires a heat labile high molecular weight plasma component. The enzyme is not inhibited to any significant degree of cholinesterase inhibitor such as physostigmine or echothiophate, but is totally inhibited by sodium fluride. No metabolic interaction has been observed between esmolol and other ester containing molecules of clinical relevance. It does not modify the magnitude or duration of neuromuscular blockade in response to succinylcholine (**Richard J. Gorzynski**) esmolol is 55 % bound to human plasma protein while acid metabolite is only 10% bound.

In human electrophysiological studies esmolol produced effects typical of a β-blocker; decreased heart rate , increase in sinus cycle length, prolongation of sinus node recovery time.

1.Esmolol produces reduction in heart rate , systolic blood pressure,

rate pressure product and right ventricular ejection fraction and cardiac index at rest and during exercise, similar in magnitude to propranolol, but produces significantly lower fall systolic in blood pressure; esmolol also produces small, clinically insignificant increase in left ventricular end-diastolic pressure and pulmonary capillary wedge pressure 30 min after discontinuation of infusion all the hemodynamic parameters return to pretreatment levels.

2.Cardioselectivity of Esmolol was demonstrated by the infusion of Esmolol in asthmatic patients which produced no significant increase in specific airway resistance compared to placebo. Unlike Esmolol, propranolol produces significant bronchospasm requiring bronchodilator therapy. Esmolol shows no adverse effects in patients with COPD.

3. Esmolol is very effective in the management of supraventricular tachycardia, atrial fibrillation and atrial flutter.

There is significant decrease in blood pressure compared to propranolol but was rapidly reversible with decreased infusion rates or on discontinuation. Hypotension was less frequent in those patients receiving concomitant digoxin.

Drug interaction

Catecholamines depleting drugs (eg reserpine) may have an additive effect

when given with Esmolol. So patients should be observed fro hypotension or

marked bradycardia.Esmolol concentrations were higher when given with warfarin but this is of no clinical importance. When given with digoxin blood levels of digoxin were higher and when given with morphine blood levels of Esmolol were higher.

Indications

For rapid control of ventricular rate as in atrial flutter or fibrillation.

For short term control of ventricular rate when short acting agents are desirable as in (SVT, unstable angina , myocardial infarction) and to control perioperative tachycardia.

Adverse Reactions

CVS- Symptomatic hypotension occours in 12% of patients. Asymptomatic hypotension in 25% of patients. Hypotension gets resolved on discontinuation of treatment. Very rarely bradycardia, chest pain, syncope, sinus pause and asystole occour all reversible with discontinuation of treatment.

CNS- Dizziness, Headache , agitation and fatigue

RS- Bronchospasm , nasal congestion – relative less

Skin- Inflammation , and induration at the site of infusion , oedema, skin discolouration, thrombophlebitis and local skin necrosis.

Acute Toxicity

Accidental massive overdose when it occours due to an error in dilution. It can cause hypotension , bronchospasm , drowsiness, bradycardia and loss of consciousness. These are resolved within ten minutes of discontinuation or with administration of pressor agents.

Compatible with commonly used intravenous fluids except $NaHCO_3$ injection.

Preparations Available

100 mg - 10 ml vial

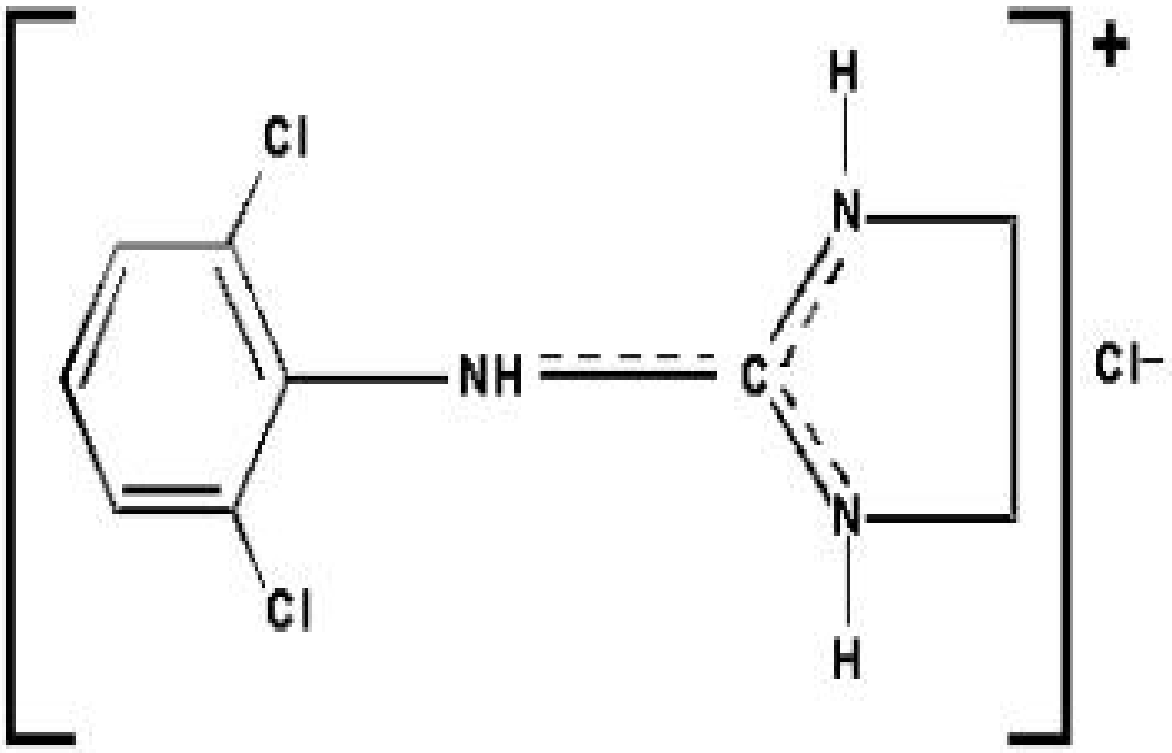
2.5 gm – 10 ml ampule

Dosage

To attenuate the sympathoadrenal response during laryngoscopy and intubation, the dosage is 1.5 mg/kg as a bolus or as an infusion at the rate of 500µg/ kg/ min for 2 minute as loading dose followed by a maintenance dose of 100µg/kg/min

To initiate treatment of a patient with supraventricular tachycardia, a loading dose of 500µg/ kg/min for 1 min for 4 minutes. If an adequate therapeutic effect is not observed within 5 min, the same loading dose can be repeated and followed with a maintenance infusion increased to 100 µg/ kg/min, therapeutic

plasma level being 400- 1200 nano gm /ml. The time to 100% recovery is 30 minutes.



$C_9H_9Cl_2N_3 \cdot HCl$ Mol. Wt. 266.56

CLONIDINE HYDROCHLORIDE

PHARMOCOLOGY OF CLONIDINE HYDROCHLORIDE

Introduction:

Clonidine hydrochloride is a centrally acting selective partial alpha -2 agonist introduced in early 1960s, it was during its use as a nasal decongestant that its anti- hypertensive property was found out. Subsequently more insights into the pharmacological properties have led to its use in clinical anaesthesia practice as well.

Clonidine hydrochloride is an imidazoline compound and exists as a mesomeric compound. The chemical name is 2-(2, 6- dichlorophenylamino)-2-imidazoline hydrochloride. The structural formula is C9H9C12N3HCl.

The molecular weight is 266.56. Clonidine is an odourless, bitter, white, crystalline substance, soluble in alcohol and water. Clonidine improves the quality of anaesthesia, provides a more stable cardiovascular course during anaesthesia and reduces the dose requirement of the anaesthetic agent. In fact clonidine may reduce the halothane MAC by upto 50% in a dose dependent manner. Clonidine potentiates the anaesthetic action of the local anaesthetics with fewer side effects in peripheral nerve blocks and central neuraxial blockade.

Availability:

Available as one ml ampoule containing 150 micrograms. It should be stored below 25^{o}c.

Mechanism of action:

Clonidine is a centrally acting selective partial α2 adrenergic agonist with a selectivity ratio of 220: 1 in favour of α2 receptors. The three subtypes of α2 receptors are α2a, α2b, α2c. α2a receptors mediate sedation, analgesia, sympatholysis . α2b receptors mediate vasoconstriction and anti- shivering. The startle response may reflect the activation of α2c receptors. The drug is lipid soluble, penetrates the blood brain barrier to reach the hypothalamus and medulla when injected epidurally. It stimulates the inhibitory α2 adrenoreceptors to reduce the central neural transmission in the spinal neurons. Inhibition of substance- P release is believed to be involved in the analgesic effect.

The α2 adrenoreceptors are located on the afferent terminals of both peripheral and spinal neurons in the superficial laminae of the spinal cord and within several brain stem nuclei implicated in analgesia. The superficial laminae contain three group of neurons: tonic, adapting, single- spike firing, all of which receive their primary sensory input from Aδ and C fibres. Studies in

rat models show that clonidine inhibits voltage gated Na+ and K+ channels and suppresses the generation of action potentials in tonic- firing spinal dorsal horn neurons, contributing to analgesic effect.

Another contribution to analgesic effect may be through the release of acetylcholine in the neuraxial region. The α2 adrenergic agonists also enhance analgesia from intraspinal opioids. Sedation is produced by its action on locus ceruleus.

Clonidine affects the blood pressure in a complex fashion after neuraxial or systemic administration because of opposing action at multiple sites. In the nucleus tractus solitarius and locus ceruleus of the brain stem, activation of post- synaptic α2 adrenoreceptors reduces sympathetic drive. It also activates nor-adrenergic imidazoline preferring binding sites in the lateral reticular nucleus producing hypotension and anti- arrythmogenic action. In the periphery it acts on pre-synaptic α2 adrenoreceptors at sympathetic terminals reduces the release of nor-epinephrine causing vasorelaxation and reduced chronotropic drive. The brainstem and the peripheral effects of α2 adrenoreceptor stimulation are counterbalanced by the direct peripheral vasoconstriction through its action on α2 adrenoreceptors from the circulating concentrations of clonidine.

As a result the dose response for clonidine by neuraxial or systemic administration is U-shaped, with peripheral vasoconstriction from circulating drug concentrations at high doses opposing central sympatholysis.

Pharmacodynamics:

The analgesic effect of clonidine is more potent after neuraxial administration indicating a spinal site of action, favours neuraxial administration, though it is possible to achieve analgesia from systemic administration as well.

General:

Clonidine is observed to be approximately twice as potent given epidurally as intravenously.

Cardiovascular system:

Clonidine has minor or no effects on responses to vasoconstrictors or atropine given to treat hypotension or bradycardia respectively, that may occur with neuraxial anaesthesia.

Sedation:

This is a desired property. Clonidine produces a dose dependent sedation at the dose of 50 mics or more in less than 20 minutes regardless of the route of administration.

Respiration:

They don’t induce profound respiratory depression even after massive overdose nor do they potentiate respiratory depression from opioids.

Peripheral nerves:

It produces a minor degree of blockade at high concentrations with some preference for

C- fibres in the peripheral nerves and this effect in part enhance the peripheral nerve block when added to local anaesthetics, probably because the α2adrenoreceptors are lacking on the axons of peripheral nerves.

Pharmacokinetics;

Clonidine is well absorbed orally and is nearly 100% bio available. The mean half life of the drug in plasma is about 12 hours. It is excreted in an unchanged form by the kidney, and its half- life can dramatically increase in the presence of impaired renal function.

A transdermal delivery system is available in which the drug is released at a constant rate for about a week. Three or four days are required to achieve steady state concentration.

Clonidine is highly lipid soluble and readily distributes into extra- vascular sites including the central nervous system.

300 micrograms intravenously over 10 min produces:

Distribution t ½ : 11 ± 9 minutes.

Elimination t1/2 : 9 ± 2 hour, 41 hours in severe renal dysfunction.

Volume of distribution : 2.1 ± 0.4 l/kg

Plasma protein binding : 20-40 % in vitro.

Metabolism : minor pathways with the major metabolite , p- hydroxyclonidine.

Excretion:

70% of the dose, mainly in the form of unchanged parent drug (40-60%) in urine.

So, the elimination t1/2 of clonidine varies as a function of creatinine clearance. In subjects undergoing hemodialysis only 5% of the body clonidine store was removed.

Adverse effects:

1. Body as a whole **:** Weakness, fatigue, headache and withdrawal syndrome, pallor, a weakly positive coomb's test and fever.

2. Cardiovascular: palpitations, tachycardia, bradycardia about 5 in 1000, syncope, raynaud's phenomenon, congestive heart failure, ECG abnormalities like sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias are reported rarely.

3. Central nervous system: nervousness, agitation, mental depression, insomnia, vivid dreams or night mares, anxiety, visual and auditory hallucinations have been reported rarely.

4. Dermatological: rash, angioneurotic edema, pruritus, urticaria and alopecia rarely.

5. Gastro intestinal tract: nausea and vomiting, anorexia, malaise, transient abnormalities in liver function tests, hepatitis, parotitis and constipation.

6. Genitourinary: decreased sexual activity, impotence, loss of libido, nocturia.

7. Hematologic: thrombocytopenia rarely.

8. Metabolic: weight gain and gynaecomastia,

9. Musculoskeletal: muscle or joint pain, leg cramps.

10. Oro-otolaryngeal: dryness of the nasal mucosa.

11. Opthalmological: dryness, burning of eyes.

Precautions:

1. In patients with renal insufficiency , lower dose is needed.
2. Sudden withdrawal of prolonged continuous epidural infusion produces hypertensive crisis. So it should be gradually discontinued over 2 to 4 days.

3. Use with caution in patients with cerebrovascular or coronary insufficiency.
4. When infused into upper thoracic spinal segments produces pronounced decrease in blood pressure.
5. If a patient with beta blocker is on continuous epidural therapy, beta blocker should be withdrawn several days before discontinuation of epidural clonidine.
6. Intrathecal / epidural clonidine often causes bradycardia that if symptomatic can be treated with inj. Atropine.

Contraindications:

1. Known hypersensitivity to clonidine or components of the product.
2. In patients with bradyarrhythmia or AV block.
3. Patients with severe cardiovascular disease
4. Patients with cardiovascular / hemodynamic instability.
5. Above C4 level is contraindicated because there are no safety data to support such use.

Interactions:

1. Clonidine may potentiate the CNS- depressive effect of alcohol, barbiturates or other sedative drugs.

2. Narcotics may potentiate the hypotensive effects of clonidine.

3. Tricyclic anti depressants may antagonize the hypotensive effects of clonidine.

4. Concomitant administration of drugs with a negative chronotropic/ dromotropic effect (beta blockers, digoxin) can cause or potentiate bradycardiac rhythm disturbances.

5. Beta blockers may potentiate the hypertensive response seen with clonidine withdrawal.

6. Epidural clonidine may prolong the duration of pharmacologic effects of epidural local anaesthetics, opioids, neostigmine and other drugs.

Indications:

1. To prolong the duration of epidural/ spinal anaesthesia and Peripheral nerve block

2. As adjuvant for the treatment of intra operative and post operative pain.

3. Treatment of intra articular intra operative and post operative pain.

4. In epidural add on agent for relief of severe cancer pain.

5. As an anxiolytic.

6. For sedation.

7. To prevent or treat shivering.

8. Treatment of hypertensive crisis

Anaesthetic uses:

1. Premedication: acting on locus ceruleus produces sedation. Also got an anaesthesia- sparing effect.

2. Control of hemodynamics: prevents hypertension and tachycardia during laryngoscopy and intubation as well as during surgical stimulation. Decreased incidence of myocardial ischemia in cardiac and vascular surgeries.

4. Epidural: as a sole agent or in combination with opioids or local anaesthetics to provide excellent analgesia in labour analgesia.

5. Spinal: with local anaesthetics clonidine improve the quality and duration of the block, minimize the tourniquet pain during lower limb surgery, and prevents shivering.

6. Caudal: with local anaesthetics increases the duration of anaesthesia and analgesia by 2 or 3 times without hemodynamic side effects. Dose 2-3 mics/kg

7. Peripheral nerve blocks: prolongs the duration of anaesthesia and analgesia with local anaesthetics by two times in a dose of 75 to150 micro grams.

8. Bier's block: 150 mics enhance the tolerance of tourniquet.

9. Intra articular analgesia.

Overdosage and treatment:

There is no specific antidote for clonidine overdosage. Supportive measures like atropine, ephedrine, i.v fluids is enough. For hypertensive crisis i.v furosemide, diazoxide, phentolamine can be used.

Yohimbine partially reverses the analgesia and sedation but not the BP and heart rate changes produced by the epidural clonidine.

Naloxone may be a useful adjunct for the management of clonidine induced respiratory depression, hypotension and or coma.

Blood pressure should be monitored after injecting naloxone as it may produce paradoxical hypertension.

REVIEW OF LITERATURE

A number of clinical studies have been undertaken in the past to assess the efficacy of Esmolol and Clonidine on haemodynamic changes.

1. Yuvesh Passi et al -J Anaesth Clin Pharmacol 2009

Fifty adult patients belonging to ASA physical status I or II, scheduled for laparoscopic Cholecystectomy were selected and randomly allocated to two groups A & B. Group A (clonidine) received Tab. clonidine 150µg orally and Group B (Control) received Tab. vitamin B complex orally as premedication 60-90 minutes before scheduled laparoscopy. Heart rate and mean blood pressure were recorded prior to intubation, 15 min after endotracheal intubation, at skin incision, 15 min and 30 min after creation of pneumoperitoneum and 15 min after release of pneumoperitoneum.

Conclusion: Premedication with oral clonidine 150 µg provides stable hemodynamics in patients undergoing laparoscopic cholecystectomy.

2. Mrinmoy et al -Indian Journal of Anaesthesia 2007

Sixty adult patients of ASA physical status I & II, scheduled for elective laparoscopic cholecystectomy were recruited for a prospective randomized, double-blinded comparative study. They were randomly allocated to one of the two groups to receive either oral clonidine 150 µg (Group C) or ranitidine 150

mg (Group P), 90 minute before induction of anaesthesia. Significant rise in heart rate was observed following pneumoperitoneum in Group P as compared to Group C. Similarly, rise in systolic arterial pressure , diastolic arterial pressure and mean arterial pressure was more in Group P following pneumoperitoneum. Incidence of postoperative nausea-vomiting and shivering was also less in Group C.

To conclude, clonidine premedication provides perioperative haemodynamic stability, hence it can be recommended as a routine premedication for laparoscopic procedure.

3.Masayoshi Uchida et al - Can J Anesth 2004

Studied 60 adult patients (ASA physical status I) were randomly assigned to one of two groups. Thirty patients received famotidine 20 mg (control group) orally 90 min before the induction of anesthesia, whereas the remaining 30 patients received clonidine 5 μg/kg and famotidine 20 mg (clonidine group). General anesthesia was induced with *iv* propofol 2 mg/kg , and tracheal intubation was facilitated with iv vecuronium 0.2 mg/kg. In 15 patients in each group, anesthesia was maintained with isoflurane 1% (end-tidal) in oxygen, and in the other 15 patients with iv propofol 100 μg/kg/min during ventilation with oxygen. MAP, CI and HR responses to hypercapnia in the clonidine-propofol subgroup were significantly attenuated compared with those in the other three subgroups. Plasma norepinephrine concentrations (but not epinephrine

concentration) were significantly lower in clonidine-propofol patient. The cardiovascular effects of hypercapnia are suppressed in patients given clonidine prior to propofol anesthesia, perhaps due to the profound suppression of sympathetic nervous system activity. The hemodynamic response to hypercapnia depends on the level and extent of any sympathetic blockade. The interaction between the basal anaesthetic agent and clonidine (given as a premedicant) can apparently modify the hemodynamic response to hypercapnia to a significant extent.

4. Yu et al - Acta Anaesthesiol Scand 2003

Thirty-two patients scheduled for elective laparoscopic cholecystectomy were recruited for a prospective, randomized, double-blinded comparative study. They were allotted randomly to two groups: placebo or clonidine. Patients in the placebo group (n = 16) were premedicated with oral antacid, while those in the clonidine group (n = 16) were premedicated with oral clonidine 150 μg before anesthesia. Analysis of heart rate variability was used to quantify the control of heart rate at baseline, and during the pneumoperitoneum and recovery periods. Time of the first request for postoperative analgesic and cumulative analgesic requirements in 24 h were recorded. Data are expressed as mean ± SD.

Conclusion: Clonidine preserves heart rate control in pneumoperitoneum and recovery periods. Oral clonidine premedication also reduces the requirement for postoperative analgesia.

5. Laisalmi et al - Surg Endosc 2001

The effects of clonidine 4.5 mg/kg or saline on hemodynamics, neuroendocrine response, and renal parameters were compared in 30 healthy patients undergoing laparoscopic cholecystectomy. Heart rate, arterial blood pressures, and plasma renin activity were lower during and after pneumoperitoneum in patients with clonidine. There were no differences in urine output, urine oxygen tension (reflecting medullary perfusion), or antidiuretic hormone between the groups. N-acetyl-b-D-glucosaminidase, a marker of proximal tubular damage, was minimally elevated after clonidine.

CONCLUSIONS: Clonidine enabled stable hemodynamics and prevented activation of RAAS seen as unchanged plasma renin activity. Clonidine may be beneficial during laparoscopy in patients with hypertension, cardiovascular, and/or renal diseases.

6.Sung et al- Acta Anaesthesiol Sin. 2000

One hundred and ten patients, scheduled for elective laparoscopic cholecystectomy, were recruited for the prospective, randomized, single-blind, comparative study. They were randomly allotted to either of the placebo or

clonidine group. Patients of the placebo group (n = 65) were premedicated with oral antacid (alugel hydroxide 300 mg), while those in the clonidine group (n = 45) were premedicated with oral clonidine 150 micrograms prior to anesthesia. The premedication was given 60 to 90 min before the anticipated time of induction of anesthesia. Normocapnia was maintained throughout the perioperative period. Mass spectrometer was used to assess the inspired and expiratory concentrations of isoflurane, the anaesthetic used for maintenance of anaesthesia. Postoperative pain intensity, sedation scores, adverse events, time to the first dose of postoperative analgesic and cumulative analgesic requirement in 24 hours were recorded.

CONCLUSIONS: Oral clonidine premedication helped to provide perioperative hemodynamic stability, spared the use of isoflurane and reduced the requirement of postoperative analgesia so as to smoother the way to recovery in patients undergoing

6.Malek et al 1999

confirmed in their work involving 21 patients the incidence of these effects and tried to suppress them by premedication with clonidine (CATAPRESAN, Boehringer). 21 patients were given 0.15 mg clonidine in an infusion 15 minutes before operation and 21patients 0.15 mg clonidine by the i.m. route 60-90 min. before operation. Standard anaesthesia was administered. A highly significant drop in the incidence of hypertension was recorded during operation

for systolic pressure ($p < 0.001$) after both ways of administration, as well as of diastolic pressure ($p < 0.01$ for intravenous and $p < 0.05$ for intramuscular premedication). Premedication with intravenous clonidine can be recommended as a routine procedure before laparoscopic cholecystectomies

7.Koivusalo and colleagues- Acta Anaesthiol Scand 1998

Found that high-dose esmolol (200 µg /kg/ min) with alfentanil effectively blunted the sympathetic response to the painful stimulus of pneumoperitoneum in ASA I and II patients, whereas alfentanil alone was ineffective. The difference in esmolol dose needed to effectively blunt sympathetic responses to intraoperative manipulation may be due to different sensitivity to ß-blockers between ethnic groups with hypertension in these studies.

9. Korpinen R - Acta Anaesthesiol Scand. 1997

conducted a double-blind study in 40 patients of ASA grade I and II. Patients were allocated to receive either Esmolol or saline under Thiopentone-Alfentanil-Isoflurane Suxamethonium anaesthesia. Esmolol in a dose of 1 mg/kg + 200 µg/kg/min was given. This study showed that in Esmolol group, neither heart rate nor the QTc interval of ECG increased when compared to baseline values. On the basis of this study it is concluded that Esmolol bolus followed by infusion is a useful treatment in circumstances where an increase in

heart rate, prolongation of QTc interval and cardiac arrhythmias are to be avoided.

10. A Vucevic (1992)

Double-blind randomized controlled study was carried in 30 ASA grade I and II patients to manage the cardiovascular stress response to tracheal intubation using Esmolol as a continuous infusion. Patients in study group received Esmolol 500 μg/kg/min for 2 minutes as a loading dose and thereafter a maintenance infusion of 100 μg/kg/min. Heart rate, systolic blood pressure, and rate pressure product were monitored and recorded at baseline, before induction and maximum after intubation. The analysis of this study showed that maximum rate pressure product recorded in association with tracheal intubation was significantly reduced in patients who received Esmolol infusion.

11. Donald Oxorn et al (1990)

A clinical study was conducted by **9** in 48 patients undergoing hysterectomy. Patients were randomly assigned to receive a single IV bolus dose Esmolol 100 mg or 200 mg or a placebo. Heart rate, systolic blood pressure and diastolic blood pressure were monitored throughout the study. They concluded that single bolus dose of 100 mg or 200 mg Esmolol was effective in ameliorating the tachycardic response to LTI. Esmolol also decreased the incidence of post-

intubation ventricular arrhythmias. No side effects attributable to Esmolol were seen.

12. Shane Sheppard et al (1990)

Conducted a study using bolus dose of Esmolol in 45 patients of ASA grade I and II undergoing various non-cardiac surgical procedures. Subjects were allocated randomly to receive Esmolol 100 mg or 200 mg IV or placebo. Changes in heart rate, systolic blood pressure were monitored at baseline, 1 minute,3 minute and 5 minute respectively. They concluded that adequate haemodynamic control was obtained following administration of 200 mg Esmolol bolus.

13. Aho et al - Anaesthesiology 1990

Ninety women undergoing gynecologic laparoscopy were randomly given clonidine 3 or 4.5 micrograms/kg or saline intramuscularly 45-60 min prior to induction of anaesthesia. Anaesthesia was induced with thiopental 3.5 mg/kg and maintained with 0.3% end-tidal isoflurane in nitrous oxide and oxygen. The laparoscopy did not begin sooner than 20 min after tracheal intubation. Arterial blood pressure and heart rate were monitored with an automatic oscillometer. When compared with the baseline values, clonidine 4.5 micrograms/kg significantly (P less than 0.001) decreased the mean arterial pressure (MAP) measured before induction of anaesthesia. In all three groups, blood pressure

and heart rate increased after tracheal intubation and after beginning of laparoscopy (P less than 0.001), but the increments were significantly greater in the control group than in the study groups. During anaesthesia alone without surgical stimulation, and again in the recovery room, MAP and heart rate were lower in the study groups than in the control group. Plasma beta-endorphin immunoreactivity (ir beta-E) was measured for ten control-group women and ten women receiving clonidine 4.5 micrograms/kg before premedication, before and after induction of anaesthesia, during laparoscopy, and 1 h after the procedure. The plasma ir beta-E increased significantly after the beginning of laparoscopy in both the control group and those given clonidine, but the increase was significantly less (P less than 0.05) in the women premedicated with clonidine. The blunting effect of clonidine on hemodynamics and plasma beta endorphin may reflect a deeper level of anaesthesia in those women receiving clonidine as preanaesthetic medication or can be explained by an interaction of clonidine with endogenous opiates. The authors conclude that intramuscularly administered clonidine premedication effectively prevents the maximal hemodynamic responses to tracheal intubation and to gynecologic laparoscopy.

14. Joris et al - Br J Anaesth 1995

Used very high dose of clonidine (8 μg/kg) for reducing the level of catecholamine and vasopressin following pneumoperitoneum conducted two

studies, each including 20 healthy patients scheduled for elective laparoscopic cholecystectomy. In the first study serial measurements of hemodynamics (thermodilution technique) were done during laparoscopy and after exsufflation. Plasma concentrations of cortisol, catecholamines, vasopressin, renin, endothelin and prostaglandins were measured at the same time points. In the second study patients were randomly allocated to receive 8μg/kg clonidine infused over 1 h or placebo before pneumoperitoneum. Hemodynamics and plasma levels of cortisol, catecholamines and vasopressin were measured during pneumoperitoneum and after exsufflation. Clonidine significantly reduced mean arterial pressure, heart rate and the increase in systemic vascular resistance. Clonidine also significantly reduced catecholamine concentrations but did not alter vasopressin and cortisol plasma concentrations.

Conclusion- Vasopressin and catecholamines probably mediate the increase in systemic vascular resistance observed during pneumoperitoneum. Clonidine before pneumoperitoneum reduces catecholamine release and attenuates hemodynamic changes during laparoscopy.

15. Lee and Lee- Korean J Anesthesiology 2010

Studied 60 patients who underwent a laparoscopic appendectomy under total intravenous anesthesia using propofol and remifentanil and compared a control group with another group that received continuously injected esmolol during anaesthesia. Postoperative 30 minute visual analog scale (VAS) scores and

diclofenac sodium use for postoperative pain control during the first 24 hours decreased significantly in the esmolol group. Also, Lee and Lee [6] adjusted the infusion rate of remifentanil to target the bispectral index (BIS) to 40-60, compared to the control group, and the total amount of remifentanil administered during approximately 57 minutes of anesthesia was significantly lower in the esmolol group. The authors attributed the decrease in postoperative pain with esmolol to its intrinsic analgesic effect, a decrease in hepatic metabolism of opioids by β-blockers to extend the analgesic effect, and a reduction in opioid tolerance.

16. T. Ozturk et al - Br J Anaesth 2008

Fourty consecutive ASA class II patients with controlled hypertension about to undergo laparoscopic cholecystectomy were randomized into two groups: an esmolol group (Group E) was given a 1 mg/ kg bolus of esmolol and a placebo group (Group P) was given an identical volume of Ringer's lactate. The rate of esmolol infusion was adjusted to keep the heart rate between 65 and 75 beats /min and was 5–10 μg/ kg /min throughout the procedure. After operation, patients reported their nausea using a four-point scale.

Conclusions. Esmolol had an opioid-sparing effect in the intraoperative and immediate postoperative period in hypertensive patients undergoing laparoscopy. When combined with alfentanil, it was more effective than placebo in decreasing early PONV.

17. Vincent Collard et al - Anesth Analg 2007

Ninety patients (consisting of three groups) were enrolled in this prospective, randomized, and observer-blinded study. The control group (*n* _ 30) received intermittent doses of fentanyl, the esmolol group (*n* _ 30) received a continuous infusion of esmolol (5–15 μg /kg/min) and no supplemental opioids during surgery, and the remifentanil group (*n* _ 30) received a continuous infusion of remifentanil (0.1– 0.5 μg /kg/min). General anaesthesia was standardized, and adjuvant medications included acetaminophen, ketorolac, local anesthetics in the skin incisions, dexamethasone, and droperidol. Postoperative analgesia included fentanyl.

CONCLUSIONS: Intraoperative IV infusion of esmolol contributes to a significant decrease in postoperative administration of fentanyl and ondansetron and facilitates earlier discharge.

18. White et al. - Anesth Analg 2003

Using gynecologic surgical model, administered 1.5μg/kg of fentanyl at induction, followed by an infusion of esmolol, and found that this group required less postoperative opioids.

19. Coloma and colleagues - Anesth Analg 2001

Found that esmolol decreased the incidence of PONV more than remifentanil after desflurane-based fasttrack anaesthesia for outpatient gynaecologic laparoscopic surgery. perioperative esmolol is an alternative to remifentanil for maintaining stable intraoperative hemodynamics. Although intravenously administered esmolol has peripheral analgesic and cardiovascular properties, it is also thought to be involved in pain modulation.

METHODOLOGY

SOURCES OF DATA

Data was collected from 90 ASA I and II patients scheduled for laparoscopic appendicectomy aged between 15-50 years at Madurai Medical College, Govt. Rajai Hospital, Madurai. Both study groups and control were selected from these patients. The study was conducted over a period of two years, August 2009 to August 2010.

INCLUSION CRITERIA

- ASA 1and ASA 2 patients.
- 15-50 age group.

EXCLUSION CRITERIA

- current treatment with a ß-blocker or calcium channel blocker
- chronic use of opioid analgesics
- history of asthma or reactive airway disease, diabetes mellitus,
- allergy to any of the medications used in the study
- obesity or cachexia beyond the ideal body weight by at least 50%
- Patients with history of hypertension, ischaemic heart disease, aortic stenosis, left ventricular failure and atrioventricular conduction block

- Patients concomitantly taking clonidine, methyl dopa, beta blocking drugs, benzodiazepines and MAO inhibitors were also excluded from the study.
- severe haemorrhage during operation or conversion to open appendicectomy
- Patients who have taken antiemetic drugs within 24 hours before surgery.
- Patients with history of neurological or renal diseases.

METHODS

The study was a prospective, randomized, double blinded one. The randomization was done using closed envelope technique.

Preanaesthetic evaluation:

1. History

2. Clinical examination

3. Relevant investigations – haemoglobin, urine analysis

4. Informed consent from patients

Preanaesthetic medication was given with tab.ranitidine 150 mg and tab.diazepam 10 mg, the night before and inj.midazolam 0.03mg/kg and

inj.glycopyrrolate 0.2 mg i.m 45 min before surgery. After shifting the patient to the operation table SpO2, NIBP, ECG monitors were attached. The baseline values were recorded. IV access was established. Patients were randomly allocated into three groups.

1) Group E – Those who receive Esmolol (0.5 mg/kg bolus 5min before induction followed by continuous infusion of 100µ/kg/min through out the surgical procedure)

2) Group C - Those who receive Clonidine (3µ/kg in 100 ml saline as infusion 15 min before induction)

3) Group D - Those who received placebo (100ml normal saline)

The drugs were given by an anaesthetist who is not involved in the study, for making the study double blinded.

Anaesthesia was induced with intravenous administration of Propofol 2mg/kg and Fentanyl 2 mcg/kg and succinylcholine chloride2 mg/kg for muscle relaxation. Proper size cuffed oral endotracheal tube was inserted. Anaesthesia was maintained with NitrousOxide 67%, Oxygen 33% and intermittent doses of inj.atracurium and inj.fentanyl. Ventilation was controlled mechanically and was adjusted to keep ETCO2 between 30 and 35 mm of Hg. The intra abdominal CO2 pressure was kept between 13-16 mm of Hg. A nasogastric tube was inserted and suction applied to empty the stomach after intubation and also before extubation.

Haemodynamic instability is defined as heart rate <60 beats min or a MABP <75 mm Hg and was treated accordingly. Systemic arterial pressure including the systolic, diastolic and mean arterial pressure, heart rate, SpO2 were recorded every 15 min, including :

(1) prior to induction

(2) three minutes after endotracheal intubation

(3) before pneumoperitoneum

(4) fifteen minutes after pneumoperitoneum

(5) thirty minutes after pneumoperitoneum

(6) ten minutes after release of CO2 and

(7) ten minutes after extubation.

Reversal of muscle relaxation was done with inj.lycopyrolate 0.01 mg/kg body weight and inj.neostigmine 0.05 mg /kg and patient was extubated. Postoperative analgesia was provided by im inj.tramadol 50 mg as required. The total number of doses of analgesic required for 12 hours was monitored.

Postoperatively all episodes of PONV experienced by the patient during the first 24 hours after anaesthesia, was recorded by direct questioning. These were assessed by a nausea and vomiting score. Rescue Antiemetic (Metoclopramide 10mg) was used if patient had nausea or vomiting and the number of doses

required was monitored. Post operative sedation of the patient was monitored for 12 hours using the ramsay sedation score.

NAUSEA AND VOMITING SCORE

No nausea - 0 No vomiting - 0

Mild nausea -1 Mild vomiting - 1

Moderate nausea - 2 Moderate vomiting - 2

Severe nausea - 3 Severe vomiting - 3

RAMSAY SEDATION SCORE:

LEVELS 1 -3 patient awake

LEVEL 1-anxious and agitated or restless or both

LEVEL 2-cooperative and oriented

LEVEL 3-responds to commands only

LEVEL 4-6 patient asleep, responds to light glabellar tap or loud auditory stimulus

LEVEL 4 –Brisk response

LEVEL 5 – Sluggish response

LEVEL 6 –No response

Statistical Methods

Information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2008).**

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

The three groups were comparable in patient characteristics like age, sex and duration of surgery

TABLE - 1

AGE DISTRIBUTION

AGE in yrs	GROUP E	GROUP C	GROUP D
RANGE	15 – 55	18 – 45	16 – 45
MEAN	27.8	27.3	29.1
S.D	8.8	6.6	8.2
P	0.6021 – not significant		

Table -1 shows that the three groups were comparable in the distribution of age.

FIGURE-1 AGE DISTRIBUTION

TABLE - 2

SEX DISTRIBUTION

SEX	GROUP E		GROUOP C		GROUP D	
	NO	%	NO	%	NO	%
MALE	9	30	11	36.7	11	36.7
FEMALE	21	70	19	63.3	19	63.3
TOTAL	30	100	30	100	30	100
p - group E &C			0.7842 – not significant			
p – group E &D			0.7842 – not significant			
p – group C & D			1.0 – not significant			

Table - 2 shows that three groups were comparable in the distribution of sex.

FIGURE-2 SEX DISTRIBUTION

TABLE -3

HEART RATE AT DIFFERENT TIME INTERVALS

HR at min	GROUP -E		GROUP- C		GROUP- D		P
	Mean	S.D	Mean	S.D	Mean	S.D	
PRE-I	86.8	8.0	88.4	10.2	85.9	12	0.597 Not significant
1	75.1	10.4	85.7	10.8	86.9	11.4	**0.0001 Significant**
5	77.0	8.6	84.3	10.6	91.1	10.3	**0.0001 Significant**
15	77.9	10.5	83.6	10.3	92.0	9.2	**0.0001 Significant**
30	78.5	10.9	84.6	9.7	91.1	8.6	**0.0001 Significant**
45	79.6	12.9	84.3	10.5	92.7	9.3	**0.0001 Significant**
60	82.6	10.1	85.4	7.0	93.9	8.5	**0.0002 Significant**
75	84	11.6	91.3	10.1	92.5	9.2	0.059 Not significant
90	88.5	13.0	89.7	10.9	84.8	4.1	0.5845 Not significant

Table-3 shows a significant difference in the heart rate between the esmolol and clonidine group as compared with the control group at 1min , 5 min, 15 min ,30 min 45 min and 60 min after intubation.

FIGURE-3 HEART RATE AT VARIOUS TIME INTERVALS

Figure 3 shows the difference in the heart rate during the inta operative period between the three groups. The (Esmolol) Group –E has a lower heart rate as compared to the (clonidine) Group- C and the Control Group - D

TABLE- 4

PERCENTAGE CHANGE IN HEART RATE FROM BASE LINE (PI) AT DIFFERENT TIME INTERVAL

%change In HR from base line rate- PI	GROUP –E		GROUP- C		GROUP- D		P
	Mean	S.D	Mean	S.D	Mean	S.D	
1	13.6	7.2	2.7	9.9	-1.4	4.5	**0.0001 Significant**
5	11.2	6.6	4.0	12.6	-6.5	6.7	**0.0001 Significant**
15	10.2	9.6	4.7	12.6	-7.9	8.5	**0.0001 Significant**
30	9.4	10.7	3.5	12.0	-6.9	9.8	**0.0001 significant**
45	8.3	12.7	3.3	13.3	-8.8	10.8	**0.0001 Significant**
60	6.5	10.5	3.4	10.3	-9.7	10.5	**0.0001 Significant**
75	5.9	10.5	-0.9	12.3	-8.2	8.8	**0.0107 Significant**
90	11.2	5.3	-6.4	12.6	-11.7	9.0	**0.0273 Significant**

Table 4 - shows a significant difference in the percentage decrease of heart rate from base line value in Esmolol group-E and Clonidine group – C as compared to control.

FIGURE 4 - PERCENTAGE OF CHANGES IN HEART RATE AT VARIOUS TIME INTERVALS

TABLE-5

SYSTOLIC BLOOD PRESSURE AT VARIOUS TIME INTERVAL

Systolic BP at min	GROUP –E		GROUP- C		GROUP- D		P
	Mean	S.D	Mean	S.D	Mean	S.D	
PRE-I	123.9	9.9	123.4	12.1	126.7	14.5	0.2355 Not significant
1	108	13.2	117	12.8	127.3	13.4	**0.0001** **Significant**
5	107.5	21.2	117.3	13.4	128.4	13.9	**0.0001** **Significant**
15	114.6	11.3	117.6	12.5	133.5	10.5	**0.0001** **Significant**
30	116.9	12.5	118.2	10.5	134.5	8.0	**0.0001** **Significant**
45	118.2	13.0	119.5	9.3	135.4	8.5	**0.0001** **Significant**
60	120.5	12.7	121.2	5.9	138	6.9	**0.0001** **Significant**
75	119.9	10.9	123	4.6	138.9	6.7	**0.0001** **Significant**
90	125.0	4.2	121.5	5.0	136.9	5.1	**0.0054** **Significant**

Table 5 - shows that there is a significant difference in the systolic blood pressure between the study groups and the control groups throughout the intra operative period.

FIGURE 5 - SYSTOLIC B.P. AT VARIOUS TIME INTERVALS

Figure 5 shows that Esmolol Group- E has significantly lower systolic blood pressure as compared to Clonidine Gruop-C and Control Group-D throughout the intra operative period.

TABLE – 6

PERCENTAGE CHANGES IN SYSTOLIC BLOOD PRESSURE FROM BASE LINE (PI) AT VARIOUS INTERVALS

% change in SBP from Pre-I at min	GROUP -E		GROUP- C		GROUP- D		P
	Mean	S.D	Mean	S.D	Mean	S.D	
1	12.9	6.7	4.9	8.5	-0.8	6.5	**0.0001 Significant**
5	12.7	16.4	4.6	10.5	-1.7	7.3	**0.0001 Significant**
15	7.2	8.9	4.4	8.7	-6	6.4	**0.0001 Significant**
30	5.4	9.8	3.8	8.0	-7	8.1	**0.0001 Significant**
45	4.3	10.2	2.6	8.9	-7.8	9.2	**0.0001 Significant**
60	4.2	8.4	1.7	7.5	-5.2	7.0	**0.0003 Significant**
75	3.2	8.1	1.2	6.2	-6.5	9.1	**0.0028 Significant**
90	5.6	4.3	4.0	6.0	-3.1	9.2	0.0942 Not significant

Table 6 - shows that there is a significant difference in the percentage of decrease in systolic blood pressure from the (pre induction) baseline value in Esmolol and Clonidine group as compared to control group.

FIGURE 6 – PERCENTAGE CHANGE IN SYSTOLIC BP AT VARIOUS TIME INTERVALS

TABLE -7

DIASTOLIC BLOOD PRESSURE AT VARIOUS TIME INTERVALS

Diastlic BP at min	GROUP -E		GROUP- C		GROUP- D		P
	Mean	S.D	Mean	S.D	Mean	S.D	
PRE-I	80.2	6.3	80.2	7.4	80.3	6.7	0.9338 Not significant
1	69.9	8.5	75.6	8.3	81.1	5.2	**0.0001** **Significant**
5	74.7	7.2	77.6	9.3	82.4	5.5	**0.0001** **Significant**
15	75.0	7.2	77.9	7.4	85.6	5.2	**0.0001** **Significant**
30	75.7	7.1	78.0	8.3	84.9	4.4	**0.0001** **Significant**
45	76.8	7.1	79.9	5.7	85.7	4.5	**0.0001** **Significant**
60	79	7.5	79.8	3.0	85.7	4.2	**0.0001** **Significant**
75	79.5	7.8	82.2	2.2	86.7	4.0	**0.0034** **Significant**
90	81.0	2.0	84.9	3.0	83.5	4.7	0.1523 Not significant

Table 7 - shows a significant difference in the diastolic blood pressure between the study groups and the control groups during the intra operative period

FIGURE 7 - DIASTOLIC B.P. AT VARIOUS TIME INTERVALS

Figure 7 shows that there is a significant difference in the diastolic blood pressure , with more decrease in the diastolic BP in the Esmolol Group-E as compared to the Clonidine Group- C and the control group- D.

TABLE- 8

PERCENTAGE OF CHANGES IN DIASTOLIC BP FROM BASE LINE VALUE (PI) AT VARIOUS TIME INTERVALS

% change in DBP from PI at (min)	GROUP -E		GROUP- C		GROUP- D		P
	Mean	S.D	Mean	S.D	Mean	S.D	
1	12.8	8.6	5.4	9.6	-1.2	5.0	**0.0001 Significant**
5	6.6	9.8	2.9	10.8	-2.9	7.0	**0.0001 Significant**
15	6.2	8.7	2.4	9.9	-6.9	6.6	**0.0001 Significant**
30	5.4	8.4	2.3	10.3	-6.1	6.8	**0.0001 Significant**
45	4.1	7.1	0.1	8.0	-6.6	5.8	**0.0001 Significant**
60	1.5	10.7	1.8	7.7	-4.5	5.4	**0.0018 Significant**
75	0.3	13.6	-1.4	5.7	-6.1	6.8	0.951 Not significant
90	1.5	6.8	1.5	6.8	-2.3	4.9	0.4138 Not significant

Table 8 - shows a significant difference in the percentage decrease in diastolic blood pressure from the base line (pre induction) value in Esmolol and Clonidine group as compared to control group.

FIGURE 8 - PERCENTAGE OF CHANGES IN DIASTOLIC B.P.
AT VARIOUS TIME INTERVALS

TABLE – 9

FENTANYL REQUIREMENT

FENTANYL REQUIREMENT	GROUP – E	GROUP - C	GROUP – D
Range	80-160	60-140	80 – 140
Mean	109.7	110.3	116.7
S.D	18.8	16.7	14.7
P	0.1461 – Not significant		

Table 9 - shows that there is no significant difference in the fentanyl requirement between the study group and the control group

FIGURE 9 - FENTANYL REQUIREMENTS (MIC)

TABLE- 10

ANTI-EMETIC DOSES

ANTI-EMETIC DOSES	GROUP – E	GROUP - C	GROUP - D
Range	0 – 2	0- 2	0- 2
Mean	0.77	0.97	1.07
S.D	0.68	0.41	0.37
P	0.0471 – significant		

Table 10 - shows that there is a significant difference in the requirement of anti emetics in the study groups and the control group

FIGURE 10 - ANTI-EMETIC DOSES

TABLE-11

SCORING OF NAUSEA AND VOMITING

SCORING OF N & V	GROUP – E	GROUP - C	GROUP- D
Range	1- 3	1-3	1-3
Mean	1.83	1.97	2.07
S.D	0.71	0.41	0.37
P	0.1836 – not significant		

Table 11 - shows that there is no significant difference in the grading of nausea and vomiting between the study groups and the control group

FIGURE 11 - SCORING OF NAUSEA AND VOMITING

TABLE – 12

POST OPERATIVE ANALGESIC REQUIREMENT

ANALGESIC REQUIREMENT	GROUP – E	GROUP- C	GRUOP- D
Range	1-3	1-3	2-3
Mean	1.9	1.57	2.4
S.D	0.55	0.63	0.5
P	0.0001 – significant		

Table 12 - shows that there is a significant difference in the requirement of post operative analgesic between the study group and the control group

FIGURE 12 - POST OPERATIVE ANALGESIC REQUIREMENT

TABLE – 13

SEDATION SCORE

SEDATION SCORE AT	GROUP – E		GROUP- C		GROUP - D		P
	Mean	S.D	Mean	S.D	Mean	S.D	
1	2.47	0.68	3.07	0.78	2.47	0.82	0.003 significant
4	2.27	0.58	2.53	0.63	2.07	0.27	0.0016 significant
6	2.1	0.4	2.1	0.4	2.03	0.18	0.7998 not significant

Table 13 - shows that there is significant difference in the post operative sedation observed at
1 hr and 4 hr between the study group and the control group. Significant difference is noted in the Clonidine Group – c

FIGURE 13 - POST OPERATIVE SEDATION

Figure 13 shows that post operative sedation is more in the Clonidine group as compared with the Esmolol group and the control group, with significant difference noted in the1st hour and the 4th hour.

DISCUSSION

Pneumoperitoneum during laparoscopy produces significant haemodynamic changes, which can be detrimental especially in elderly and haemodynamically compromised patients. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum. This double blind prospective study was carried out in 90 adult patients, to evaluate the effect of Esmolol and clonidine in attenuating haemodynamic stress response associated with pneumoperitoneum. Esmolol is the first intravenous, short-acting, titratable β-blocker available for use in critical care and surgical settings. Esmolol is thought to be a "jack of all trades" among drugs used in anesthesia because it prevents and treats cardiovascular responses due to perioperative stimuli.

Shane Sheppard et al in 1990 found that a bolus of 200mg Esmolol was adequate to produce hemodynamic stability in patients undergoing non cardiac surgical procedures.

A vucevic in 1992 found that a loading dose of 500µg/kg/min for 2 min followed by a infusion of 100µg/kg/min reduced the intubation stress and maintained hemodynamic stability.

Koivusalo et al in1998 found that high dose Esmolol (200µ/kg/min) with alfentanyl effectively blunted the hemodynamic response to pneumoperitonium.

Korpinen in 1997 found that a bolus dose of 1mg/kg of Esmolol followed by a infusion 200µ/kg/min was useful in circumstances were a increase in heart rate and cardiac arrhythmias are avoided.

In my study i used a bolus dose of 0.5 mg/kg of Esmolol 5 min before induction followed by a infusion of 100µ/kg/min through out the surgical procedure, it was observed that there was a significant reduction in the heart rate throughout the procedure, mean value of 78.5 ± 10.9 ,the mean range 75.1 ± 10.4 to 88.5 ± 13.0 and the percentage reduction from the baseline value (pre induction) varied from a mean value of 13.6± 7.2 to 6.5± 10.5. Out of the 30 cases studied 3 patients had bradycardia with heart rate less than 60 and required reduction in the dose of Esmolol infusion.

There was also a significant difference in the systolic blood pressure in the Esmolol group as compared with the control throughout the procedure. The mean systolic blood pressure was 116.9 ± 12.5, and was kept in the range of 108 ±13.2 to 125 ± 4.2. The percentage reduction in the mean systolic BP observed was 5.4 ± 9.8, with a maximum reduction of 12.9 ± 6.7.

There was also a significant difference in the diastolic blood pressure, with a mean BP of 75.7 ± 7.1.Mean ranging from 69.9 to 81.0.

Ozturk et al had observed a opioid sparing effect with intra operative use of Esmolol, in my study i didnot observe any significant reduction in the intra operative fentanyl requirement.

Ozturk et al (2008) and Coloma et al (2001) observed that Esmolol produced a reduction in the incidence of PONV in patients undergoing laproscopic surgeries. In my study i observed that there was a significant reduction in the anti emetic requirement in the post operative period with a mean value of 0.77 , requirement ranging from 0 to 2, out of 30 patients studied 8 patients didnot require any anti emetic post operatively and only one patient required 2 doses of anti emetic. Maintaining a stable intraoperative blood pressure has been found to be an effective method of preventing PONV.

Ozturk et al (2008), White et al (2001), Lee and lee (2010) found that intra operative use of Esmolol reduced the post operative analgesic or opioid requirement. In my study i observed a significant reduction in the post operative analgesic requirement in the patients who received intra operative Esmolol as compared with the control group. The mean requirement of 1.9 ± 0.55 and the control group requiring 2.4 ± 0.5. The hippocampus plays a role in nociception, a role predicated, on *n*-methyl-d-aspartate receptors. It then seems possible that the activation of hippocampal β-adrenergic receptors might play a role in nociceptive processes. If so, then blockade of these receptors should blunt the

contribution of such β-adrenergic activation to the nociceptive process, thereby resulting in the attenuation of perceived pain intensity.

Clonidine, an imidazoline derivative is a selective α2 adrenergic agonist. It is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased SVR and cardiac output. Clonidine inhibits the release of catecholamine and vasopressin and thus modulates the haemodynamic changes induced by pneumoperitoneum.

Aho et al used 3 μg/kg and 4.5 μg/kg clonidine for suppression of haemodynamic response to pneumoperitoneum. Joris et al used very high dose of clonidine (8 μg/kg) for reducing the level of catecholamine and vasopressin following pneumoperitoneum. Malek et al used 150 μg of clonidine as i.v. infusion and intramuscularly while Sung et al and Yu et al used 150 μg of oral clonidine as premedication for maintenance of haemodynamic stability during pneumoperitoneum.

In my study i used 3μ/kg of Clonidine as infusion 15 minutes before induction, there was a significant reduction in the heart rate throughout the intra operative period with a mean of 84.6 ± 9.7 , the range of intra operative heart rate was 83.6 ±10.3 to 91.3 ± 10.1 there was also a significant diference in the

percentage fall from the pre induction value , with a mean percentage fall of 4.7 ± 12.6 .

In my study there was a significant reduction in the systolic BP as compared with the control group, with mean systolic BP of 118.2 ± 10.5, the range of systolic BP observed was 117 ± 12.8 to 123.4 ± 12.1. There was also a significant percentage decrease in the systolic BP from the base line pre induction value as compared with the control, with a mean percentage decrease of 3.8 ± 8.0, with a maximum reduction of 4.9 ± 8.5.

There was also a significant reduction in the diastolic BP as compared to the control with a mean of 78.0 ± 8.3, mean ranging from 75.6 ± 8.3 to 84.9 ± 3.0 .

Clonidine interacts with the endogenous opiates beta-endorphins. The plasma level of beta-endorphins increases significantly after laproscopy. The blunting effect of clonidine on hemodynamics and plasma beta-endorphins may reflect a deeper level of anaesthesia in those receiving Clonidine.

There was a reduction in the PONV in patients receiving Clonidine , with a mean anti emetic requirement of 0.97 ± 0.41 as compared to control with a mean value of 1.07 ± 0.37 ,out of 30 patients receiving Clonidine 10 patients did not require any antiemetic and 2 patients required two doses of antiemetic.

Marimony et al (2007) found a decreased incedence of nausea and vomiting in patients receiving Clonidine. Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic outflow from the central nervous system. Although many workers have reported the antiemetic property of clonidine, the mechanism by which it acts warrants further investigation.

Sung et al (2000) and Yu et al (2003) found that preoperative clonidine admistration reduced the post operative analgesic requirement. In my study there was a significant reduction in the post operative analgesic requirement in patients receiving clonidine. The mean analgesic dose requirement was 1.57 ± 0.63 as compared to control group requiring 2.4 ± 0.5.

In my study the post operative sedation score was observed for 6 hrs postoperatively and was found that clonidine group had a significantly high sedation score at 1 hr and 4 hr after the surgery. The mean sedation score at 1 hr was 3.07 ± 0.78 and at 4 hrs 2.53 ± 0.63.

When compared with Esmolol and clonidine the intraoperative heart rate, systolic BP , Diastolic BP was better maintained with Esmolol Group Than with the clonidine Group. The mean heart rate maintained in the range of 75.1 ± 10.4

to 88.5 ± 13.0 in the Esmolol group and 83.6 ±10.3 to 91.3 ± 10.1in the clonidine group. The mean systolic BP in Esmolol group was in the range of 108 ±13.2 to 125 ± 4.2 and in clonidine group was in the range of 117 ± 12.8 to 123.4 ± 12.1. It was found to be statistically significant.

It was observed that post operative anti emetic requirement was significantly less in both Esmolol and Clonidine group. The requirement was more reduced in the Clonidine group as compared to Esmolol group, but the difference was not found to be statistically significant.

Post operative analgesic requirement was also observed to be significantly lower in Esmolol and Clonidine group as compared to the control group. It was found to be more decreased in clonidine group than with Esmolol group, but the comparison found no significant statistical significance.

Post operative sedation was more with clonidine group as compared to Esmolol and Control group. Esmolol group didnot have any significant increase in the post operative sedation as compared to control.

No adverse effect was observed with the study group during the intra operative and post operative period.

Some limitations with the design of the study. First, the anaesthesiologists who administered the anaesthetics might have been biased in the administration of the study drugs. Second, it is argued that the use of a BIS monitor would have ensured that the three groups had similar depth of anaesthesia.

SUMMARY

Hemodynamic changes during laproscopic surgery is attributed to the stress response to pneumoperitonium.

We studied ninety patients of both sexes coming to Madurai Medical College hospital for elective laparoscopic appendicectomy. The patients were randomized in to three groups to receive intravenously Esmolol 0.5µg/kg bolus followed by infusion of 100µ/kg/min or Clonidine 3µg/kg or placebo just before induction of anaesthesia. They were induced with propofol, succinyl choline, fentanyl was used as the intra operative analgesic. Anaesthesia was maintained with Nitrous oxide and Oxygen. Patients were observed for intra operative heart rate, systolic BP, diastolic BP. Hemodynamic stability was defines as heart rate in the range of 60 to 100 and blood pressure fall or rise not more than 15% from base line.

Both Esmolol and Clonidine were effective in producing intra operative hemodynamic stability as compared to the control group by blunting the stress response to pneumoperitonium. No difference in adverse events was observed in the two groups.

In addition , Esmolol and Clonidine were found to reduce the incidence of PONV and post operative analgesic requirement.

CONCLUSION

Incidence of hemodynamic changes during laproscopic procedure is proven, and various methods of stress attenuation to pneumoperitonium is adviced. I decided to study the efficacy of Esmolol and Clonidine in maintaining hemodynamic stability in patients undergoing laproscopic appendicectomy. After premedication, patients were administered the study drugs intravenously prior to the induction and balanced general anaesthesia was administered. Patients were observed for intra operative hemodynamic stability which included heart rate, systolic and diastolic blood pressure. The study group was compared with a control group who received placebo.

It was obsereved that a bolus dose of Esmolol of 0.5 mg/kg pre induction followed by an infusion of 100μ/kg/min during intra operative period or a pre induction dose of Clonidine 3μ/kg attenuated the hemodynamic stress produced by pneumoperitonium and produced intra operative hemodynamic stability. It was observed that Esmolol produced better hemodynamic stability than Clonidine.

I conclude that both Esmolol and Clonidine produces hemodynamic stability for laproscopic appendicectomy, with more reduction in heart rate and blood pressure with Esmolol than Clonidine.

Additional observations were:

- Both Esmolol and Clonidine reduced the incidence of post operative nausea and vomiting, more reduced with Esmolol.

- Both Esmolol and Clonidine reduced the post operative analgesic requirement , more reduced with Clonidine.

- Clonidine produced post operative sedation,were as Esmolol didnot have any sedative effect.

BIBLIOGRAPHY

1.Aho M, Scheinin M, Lehtinen AM, et al. Intramuscularly administered dexmedetomidine attenuates haemodynamic and stress responses to gynaecologic laparoscopy. Anesth Analg 1992; 75: 932-9.

2.Coleman A.J. and Jordan. C. (1980) Cardiovascular response to anaesthesia-influence of β- blockade with metaprolol. Anaesthesia 35 : 973

3. Coloma M, Chui JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast track outpatient gynaecologic laparoscopic surgery. Anesth Analg. 2001;92:352–357.

4. Chia YY, Chan MH, Ko NH, Liu K. Role of beta-blockade in anaesthesia and postoperative pain management after hysterectomy. Br J Anaesth 2004; 93: 799-805.

5.Edmund H Sonnerblick (1985) – A symposium on Esmolol as ultrashort acting intravenous beta blocker. American journal of cardiology Oct 56: 1F to 60 F

6.Donald R. Miller, Raymond . Martinean (1989)- Bolus administration of Esmolol for treatment of intraoperative myocardial ischemia. Canadian Journal of anaesthesiology 1989- 36:5, 593-597.

7.Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML. Hemodynamic changes during laparoscopic cholecystectomy. *Anesth Analg*. 1993;76:1067-1071

8.Joris J, Chiche JD, Lamy M. Clonidine reduced haemodynamic changes induced by pneumoperitoneum during laparoscopic cholecystectomy. Br J Anaesth 1995; 74 (suppl) : A124.

9. Koivusalo AM, Scheinin M, Tikkanen I, Yli-Suomu T, Ristkari S, Laakso J, Lindgren L. Effects of esmolol on haemodynamic response to CO2 pneumoperitoneum for laparoscopic surgery. Acta Anaesthesiol Scand 1998;42:510–7

10. Laisalmi M, Koivusalo AM, Valta P, Tikkanen I, Lindgren L. Clonidine provides opioid-sparing effect, stable haemodynamics and renal integrity during laparoscopic cholecystectomy. Surg Endosc 2001; 15: 1331-5.

11. Lee SJ, Lee JN. The effect of perioperative esmolol infusion on the postoperative nausea, vomiting and pain after laparoscopic appendectomy. Korean J Anesthesiol 2010; 59: 179-84.

12.Lippincott Williams and Wilkins Publishers 2006, 4th ed

13. Mealy K, Gallagher H, Lennon F, Traynor O, Hyland J. Physiological and metabolic responses to open and laparoscopic cholecystectomy. *Br J Surg*. 1992;79:1061–1064

14. Mrinmoy Das1,Manjushree Ray2, Gauri Mukherjee3, haemodynamic changes during laparoscopic cholecystectomy: effect of clonidine premedicationindian journal of anaesthesia 2007;51 (3) : 205-210.

15. Malek KJ, Knor J, Kurzova A, Lopourova M. Adverse haemodynamic changes during laparoscopic cholecystectomy and their possible suppression with clonidine premedication. Comparison with intravenous and intramuscular premedication. Rozhl Chir 1999; 78 : 286-91.

16.Miller D.R. Martinean R.J. (1991) – Esmolol for control of hemodynamic responses during anesthetic inductions. Canadian Journal of Anaesthesia S 164

17. Miller`s Text book of Anaesthesiology 7th ed , Elsevier's publishers , chapter68

18. O'Leary E, Hubbard K, Tormey W, Cunningham AJ. Laparoscopic cholecystectomy: hemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position. *Br J Anaesth*. 1996;76:640–644

19.Peter Dzendrowski. Anaesthesia for laparoscopic surgery, September 1999; (Cited January 18, 2007). Available from URL: http://www.aic.cuhk.edu.hk/web8/laparoscopic_surgery.htm

20.Richard J. Gorczynski (1985) – A Symposium on Esmolol – An ultrashort acting intravenous β- blocker. The American Journal of Cardiology Oct- 56, 1F to 60F

21.Robert K. Stoelting. Pharmacology and Physiology in anaesthetic practice,

22. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2000; 38 : 23-9.

23. Tripathi KD. Essentials of Medical Pharmacology, New Delhi, Jaypee Br2others Medical Publishers (P) Ltd. 2003.

24. vincent collard md, giovanni mistraletti, md,ali taqi, md,juan francisco asenjo, md,liane s. feldman, md,gerald m. fried, md,franco carli, md, mphil,intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy anesthesia & analgesia vol. 105, no. 5, november 2007,

25. Yoon Hee Kim, Department of Anesthesiology and Pain Medicine, Chungnam National University School of Medicine, Daejeon, Korea, The antinociceptive effect of esmolol, Korean J Anesthesiol 2010 September 59(3): 141-143

26. Yu HP, Hseu SS, Yien HW, TengYH, Chan KH : Oral clonidine premedication preserves heart rate variability for patients undergoing laparoscopic cholecystectomy. ActaAnaesthesiol Scand 2003; 47 : 185-90.

PROFORMA-GROUP-

NAME AGE IP NOWT

PRE MED- Glycopyrrolate 0.2mg & Midazolam- 0.03 mg/kg

PRE INDUCTION - Study drug / Placebo

INDUCTION- Propofol 2mg/kg Fentanyl 2 mics/kg Suxa 2mg/kg

MAINTANANCE- Oxygen:NitrousOxide 2:3 , Atracurium, Fentanyl -20mics half hrly (if additional analgesic required suppl with 10 mics)

(Group E - 100 mics/kg/min infusion)

MONITORING PARAMETERS

	PR	SBP	DBP
Pre-induction/ Base line			
1 min			
5min			
15min			
30 min			
45 min			
60 min			
75min			
90 min			
105min			
120 min			

REVERSAL- Neostigmine- 0.5mg/kg

Glycopyrrolate- 0.01mg/kg

TOTAL FENTANYL REQUIREMENT -

PONV – 1hr- 4hr- 6 hr-

NO OF ANTI-EMETIC DOSES -

NO OF ANALGESIC DOSES –

SI NO	NAME	AGE	SEX	HR-PI	HR-1MIN	HR-5MIN	HR-15MIN	HR-30MIN	HR-45MIN	HR-60MIN	HR-75MIN	HR-90MIN	HR-105 MIN	SBP-PI	SBP-1MIN	SBP-5MIN	SBP-15MIN	SBP-30MIN	SBP-45MIN	SBP-60MIN	SBP-75MIN	SBP-90MIN	SBP-105 MIN	SBP-120MIN
1	LAKSHMI	15	F	83	66	80	98	102	112	100				110	90	105	120	126	137					
2	PONPAITHI	40	F	90	86	92	96	98	98	100	112			112	89	100	116	114	120	130	130			
3	SELVARANI	15	F	100	100	90	82	78	78					124	120	84	86	84	90					
4	SUBHAMMAL	55	F	92	84	72	68	64	68	64				130	110	100	90	98	98	100				
5	BABU	19	M	90	96	98	102	100	100	100				120	100	100	110	110	110	110				
6	NAGAJYOTHI	34	F	78	72	70	72	74	72	74	70			100	90	92	100	105	100	105	100			
7	THAMILARASU	30	M	90	88	72	74	78	88	87	90			130	120	100	120	130	150	140	138			
8	PANDI	35	M	75	60	72	72	74	62					120	90	110	120	130	120					
9	GAYATHRI	25	F	82	68	72	78	74	70	72				120	100	110	110	100	100	100				
10	VIMALA	30	F	84	68	70	72	70	74	76	70			120	100	110	110	100	100	96	100			
11	CHELLAMMA	26	F	92	74	78	82	84	86	82	90			130	110	110	120	116	120	120	116			
12	PANDIAN	30	M	88	72	78	80	84	86	84	82			120	100	110	110	116	120	120	116			
13	SHARADHA	32	F	86	69	72	74	78	79	82	86			130	100	110	110	120	120	130	126			
14	HAJA MOHAMMED	35	M	94	74	78	84	84	86	88	88	90		140	100	110	110	110	126	130	120	126		
15	REKHA	21	F	78	62	68	70	72	72	78				120	110	118	118	120	118	120				
16	RAJU	18	M	80	72	74	70	73	78					120	110	112	118	120	120					
17	PICHAIAMMAL	40	F	87	74	72	70	68	72	74	80			120	108	110	116	112	116	118	120			
18	SHEELA	17	F	78	60	62	64	69	72					110	90	100	108	110	112					
19	VALLIAMMAI	28	F	98	80	90	88	82	88	90	94	88		130	120	124	120	124	124	126	120	120		
20	RAJAPANDI	31	M	92	80	82	80	82	84	82				130	120	124	126	126	130	120				
21	MARY	18	F	72	62	64	68	70	72					110	100	100	112	116	116					
22	JAYALAKSHMI	27	F	102	90	88	92	94	92	94				140	130	132	134	140	130	130				
23	FATHIMA	28	F	98	78	80	84	86	84	84	88	82		130	120	124	124	124	120	124	126	124		
24	BALAMURALI	34	M	94	80	82	80	84	90	88				140	130	13	126	130	134	140				
25	JAMUNA	31	F	84	78	79	80	82	84	88	84	84		130	130	130	132	134	130	132	134			
26	AZHAGI	26	F	84	76	78	70	72	68	72	70			120	100	110	112	112	110	110	116			
27	ANJALI	18	F	74	64	68	62	58	52	68	68			120	100	112	104	108	112	114	110			
28	BALASUBRAMANIAM	19	M	78	62	68	58	58	54	68				120	102	112	100	110	110	112				
29	PARAMESHWARI	31	F	88	78	80	82	82	84	88				140	126	128	130	132	134	140				
30	SHANMUGAPRIYA	26	F	93	80	82	84	82	84	82	88	80	88	130	124	126	126	130	120	124	126	130	130	130

SI NO	NAME	AGE	SEX	DBP-PI	DBP-1MIN	DBP-5MIN	DBP-15MIN	DBP-30MIN	DBP-45MIN	DBP-60MIN	DBP-75MIN	DBP-90MIN	DBP-105MIN	FENTANYL REQUIREMENT(MIC)	NO OF DOSES OF ANTI-EMITIC	SCORING OF N &V	POST OP ANALGESIC REQUIREMENT	SEDATION SCORE-1HR	SEDATION SCORE-4HR	SEDATION SCORE-6HR
1	LAKSHMI	15	F	70	50	90	70	70	70					80	1	1	2	3	2	2
2	PONPAITHI	40	F	74	56	60	66	77	70	90	90			120	NIL	1	2	3	2	2
3	SELVARANI	15	F	84	80	68	64	64	60					80	1	2	2	2	2	2
4	SUBHAMMAL	55	F	78	60	62	64	62	64	60				120	1	2	3	2	2	2
5	BABU	19	M	80	70	70	70	70	80	80				100	NIL	1	2	2	2	2
6	NAGAJYOTHI	34	F	70	60	60	60	60	64	68	70			80	1	2	2	4	3	2
7	THAMILARASU	30	M	70	70	70	76	75	70	90	90			160	NIL	1	1	2	2	2
8	PANDI	35	M	80	60	70	70	70	70					100	NIL	1	2	3	2	2
9	GAYATHRI	25	F	70	60	70	66	66	70	70				120	1	2	2	2	3	2
10	VIMALA	30	F	80	70	70	60	60	70	80	60			120	1	2	2	2	2	4
11	CHELLAMMA	26	F	80	70	80	80	76	76	70	80			100	1	3	2	2	4	2
12	PANDIAN	30	M	80	60	70	80	80	80	70	80			120	NIL	1	2	3	2	2
13	SHARADHA	32	F	90	60	70	80	80	86	90	86			100	1	2	2	2	2	2
14	HAJA MOHAMMED	35	M	90	70	80	70	80	86	80	70	90		120	1	2	2	2	2	2
15	REKHA	21	F	70	64	70	72	74	74	74				100	2	3	1	2	2	2
16	RAJU	18	M	80	70	80	80	80	80					90	NIL	1	3	2	2	2
17	PICHAIAMMAL	40	F	80	80	80	80	80	80	80	82			140	1	2	2	4	3	2
18	SHEELA	17	F	80	70	80	80	80	80					100	1	2	1	3	4	2
19	VALLIAMMAI	28	F	90	80	80	80	80	82	80	80	80		120	1	2	2	2	2	2
20	RAJAPANDI	31	M	90	80	80	80	84	80	80				100	1		1	3	2	2
21	MARY	18	F	80	76	78	80	78	78					90	NIL	1	2	2	2	2
22	JAYALAKSHMI	27	F	90	80	84	84	80	82	80				120	2	3	2	3	2	2
23	FATHIMA	28	F	80	76	78	80	78	80	82	82	80		140	2	3	2	4	3	2
24	BALAMURALI	34	M	80	74	78	80	80	82	80				120	1	2	2	2	2	2
25	JAMUNA	31	F	80	80	80	82	84	82	83	80			120	NIL	1	2	2	2	3
26	AZHAGI	26	F	80	72	76	78	78	80	78	78			100	1	2	1	2	2	2
27	ANJALI	18	F	80	72	70	74	78	80	78	80			90	1	2	3	2	2	2
28	BALASUBRAMANIAM	19	M	80	70	74	78	80	78	80				100	NIL	1	1	3	2	2
29	PARAMESHWARI	31	F	90	80	80	82	84	90	90				120	2	3	2	2	2	2
30	SHANMUGAPRIYA	26	F	80	78	82	84	82	80	82	84	84	80	120	1	2	2	2	2	2

ESMOLOL-SHEET 2

SL NO	NAME	AGE	SEX	HR-PI	HR-1 MIN	HR-5 MIN	HR-15 MIN	HR-30 MIN	HR-45 MIN	HR-60 MIN	HR-75 MIN	HR-90 MIN	HR-105 MIN	SBP-PI	SBP-1 MIN	SBP-5 MIN	SBP-15MIN	SBP-30 MIN	SBP-45 MIN	SBP-60 MIN	SBP-75 MIN	SBP-90 MIN	SBP-105 MIN	SBP-120 MIN
1	KANNAN	41	M	100	70	60	58	62	64					160	140	140	140	130	136					
2	NAGARAJAN	23	M	90	94	84	80	82	86	86				120	90	90	100	110	110	120				
3	VELMURUGAN	25	M	96	82	84	86	82	84	86				124	90	90	92	106	110	110				
4	MOHAMMED	18	M	88	82	80	82	80	78	78				110	105	100	102	104	104	108				
5	KAVITHA	22	F	98	92	90	92	90	94					110	100	90	92	90	94					
6	KALAVANI	28	F	98	94	90	88	82	84	80				140	130	120	130	134	126	124				
7	ARUMUGAM	31	M	84	94	92	88	90	82	88				130	132	130	120	124	120	124				
8	INDRA	27	F	84	82	95	94	88	82	88				110	112	116	116	112	114	120				
9	VELUCHAMI	31	M	72	74	80	74	72	71					110	112	114	110	112	116					
10	HABEEBA	34	F	94	98	102	98	97	94	88	88			130	134	136	130	126	120	124	120			
11	SULTHANA	28	F	112	116	101	98	94	96	94	98			120	126	124	130	132	126	124	124			
12	INDRANI	26	F	102	104	101	98	94	92	88	94			120	126	128	130	132	134	130	120			
13	BANUMATHI	26	F	98	99	94	92	88	82					120	126	124	124	120	120					
14	KURUVAMMAL	34	F	80	82	84	80	82	84	86				110	114	116	120	120	124	120				
15	MANGALAM	30	F	72	82	84	80	76	78	80	82	82		120	124	126	130	128	126	130	130	124		
16	KALA	19	F	100	93	94	74	98						124	100	96	100	110						
17	MUTHU	18	M	73	80	63	63	79	93					105	100	126	96	100	125					
18	BAKYAM	33	F	92	74	74	82	84	84	86	82	82		140	120	126	130	126	124	126	124	124		
19	MEENAKSHI	21	F	82	84	88	92	90	88	84				120	110	114	116	114	120	120				
20	BARVEEN	22	F	72	76	78	80	80	82					110	112	114	114	118	112					
21	KASTHURI	20	F	78	76	82	84	80	80	84				120	112	115	118	118	116					
22	LAKSHMI	34	F	92	98	98	100	112	112	100	112	108		130	134	130	128	124	128	124	126	124		
23	KANAGAMMAL	45	F	92	84	80	78	79	80	82				140	130	132	124	126	120	120				
24	MUTHAIAH	24	M	90	92	88	94	98	110	102	98			120	116	105	124	126	128	126	128			
25	BARHATH NISHA	29	F	84	80	82	88	90	82					130	120	124	122	120	124					
26	CHELLAPPA	34	M	80	68	72	70	78	68	72				120	118	120	116	118	120	120	120			
27	PONUTHAI	28	F	84	80	78	84	80	78					140	124	126	124	120	124					
28	DINESH	18	M	78	80	82	78	76	74	82	84	82		118	112	108	114	102	100	112	114	114		
29	VIGNESHWARAN	25	M	90	82	80	78	80	84	80	84			130	124	120	124	126	124	120	124			
30	RAJATHI	26	F	98	78	68	74	76	78	80				120	116	118	112	118	120					

CLONIDINE- SHEET1

L NO	NAME	AGE	SEX	DBP-PI	DBP-1MIN	DBP-5MIN	DBP-15MIN	DBP-30MIN	DBP-45MIN	DBP-60MIN	DBP-75MIN	DBP-90MIN	DBP-120 MIN	FENTANYL REQUIREMENT(MIC)	NO OF DOSES OF ANTI-EMITIC	SCORING OF N &V	POST OP ANALGESIC REQUIREMENT	SEDATION SCORE-1HR	SEDATION SCORE-4HR	SEDATION SCORE- 6HR
1	KANNAN	41	M	100	90	100	90	90	92					130	1	2	1	4	2	2
2	NAGARAJAN	23	M	80	60	60	60	60	70	80				120	NIL	1	1	4	3	2
3	VELMURUGAN	25	M	92	60	60	62	64	70	70				140	1	2	2	4	3	2
4	MOHAMMED	18	M	70	70	68	68	70	72	74				100	NIL	2	2	3	2	2
5	KAVITHA	22	F	70	60	60	64	62	64					100	1	2	2	3	2	2
6	KALAVANI	28	F	90	90	90	84	86	88	84				120	NIL	2	1	2	2	2
7	ARUMUGAM	31	M	90	82	84	86	90	86	84				120	NIL	2	2	3	2	2
8	INDRA	27	F	80	78	80	82	82	82	80				120	1	2	1	2	2	2
9	VELUCHAMI	31	M	70	70	72	76	76	78					120	NIL	1	2	3	2	2
10	HABEEBA	34	F	80	80	82	82	84	86	82	86			120	1	2	2	4	3	2
11	SULTHANA	28	F	80	82	82	80	82	80	80	80			100	2	3	2	4	3	2
12	INDRANI	26	F	78	78	80	80	80	80	80	86			100	1	2	1	4	2	2
13	BANUMATHI	26	F	70	78	80	80	78	82					100	NIL	2	1	3	3	2
14	KURUVAMMAL	34	F	70	72	80	80	78	78	80				120	1	2	3	2	2	2
15	MANGALAM	30	F	80	80	86	84	86	84	80	82	80		120	1	2	1	2	4	3
16	KALA	19	F	76	60	56	66	64						60	1	2	1	2	3	2
17	MUTHU	18	M	76	70	80	70	60	80					80	NIL	2	2	3	2	2
18	BAKYAM	33	F	90	80	82	82	80	84	80	80	80		120	1	2	2	2	2	2
19	MEENAKSHI	21	F	80	70	78	86	80	80	80				100	1	2	1	3	3	2
20	BARVEEN	22	F	70	68	72	74	76	76					100	1	2	1	3	3	2
21	KASTHURI	20	F	80	74	74	78	80	80					100	1	2	3	3	2	2
22	LAKSHMI	34	F	80	82	84	82	84	82	80	82	84		120	NIL	2	2	4	2	2
23	KANAGAMMAL	45	F	90	78	80	80	82	84	80				100	1	2	2	4	2	2
24	MUTHAIAH	24	M	80	787	82	80	80	78	82	82			120	NIL	2	1	3	3	2
25	BARHATH NISHA	29	F	80	78	76	78	80	80					100	1	2	2	3	4	2
26	CHELLAPPA	34	M	84	80	82	84	82	80	80	82			140	1	2	1	4	3	2
27	PONUTHAI	28	F	80	78	82	80	82	80					120	2	3	1	4	3	2
28	DINESH	18	M	80	78	80	82	80	78	80	82	80		100	NIL	2	2	3	3	4
29	VIGNESHWARAN	25	M	80	76	78	78	80	82	80	80			120	NIL	1	1	2	2	2
30	RAJATHI	26	F	80	80	78	80	82	80	80				100	1	2	1	2	2	2

CLONIDINE- SHEET2

SL NO	NAME	AGE	SEX	HR-PI	HR-1MIN	HR-5MIN	HR-15MIN	HR-30MIN	HR-45MIN	HR-60MIN	HR-75MIN	HR-90MIN	HR-105MIN	SBP-PI	SBP-1MIN	SBP-5MIN	SBP-15MIN	SBP-30MIN	SBP-45MIN	SBP-60MIN	SBP-75MIN	SBP-90MIN	SBP-105MIN	SBP-120MIN
1	KUPPUSAMY	30	M	70	76	72	70	66	68	78	74	70		140	120	100	130	140	146	146	150	130		
2	SUBBIAH	34	M	88	84	90	94	86	82	100	102	100		130	130	140	140	130	140	140	130	130		
3	MANIARASU	45	M	64	62	66	72	74	64	68	78	82		140	130	140	150	150	140	140	140	140		
4	SREENIVASAN	32	M	78	82	89	90	94	92	94				140	136	138	140	146	144	140	142			
5	BALAKRISHNAN	28	M	92	94	96	98	100	94	98	98			120	120	130	130	134	150	136	134			
6	RAMU	34	M	96	94	92	90	94	98	92	90			140	146	140	150	140	140	140	150	150		
7	VELLAISAMY	25	M	66	68	72	78	78	80					130	136	138	138	136	134					
8	ARJUN	18	M	98	100	102	98	96	98	100	98	98		110	112	120	128	130	132	136	138	136		
9	MARUDUPANDI	34	M	78	74	78	80	90	86	84	90	96		140	140	136	140	136	138	140	136	138		
10	KARUPPIAH	24	M	82	88	90	86	80	90	92	88			130	120	130	130	140	130	130	134			
11	LOGESHWARI	17	F	110	100	104	98	108	104	100	106			100	90	110	120	126	130	124	128			
12	KASIAMMAL	21	F	78	80	92	94	88	96					120	128	124	130	132	130					
13	SELVI	18	F	96	98	100	104	94	90	94	96			140	140	136	138	140	142	144	142			
14	PREMA	21	F	88	90	92	96	90	96					120	124	120	128	130	134					
15	JYOTHI	31	F	80	84	88	82	84	86	90	94	96		140	140	136	138	140	142	146	140	142		
16	TAMILSELVI	36	F	86	88	90	92	98	96	98				140	140	146	138	140	142	140				
17	SUMATHI	19	F	92	92	102	98	96	98					100	110	102	120	124	126					
18	SELVAJYOTHI	22	F	110	112	100	108	98	104	100				120	124	108	130	126	128	130	132			
19	POONGODI	16	F	102	110	108	100	98	104	110				90	112	100	104	116	118					
20	RANI	39	F	78	84	88	90	92	98	96				140	146	140	148	144	142	146				
21	VIJAYA	36	F	80	84	90	88	90	92	94				140	144	146	148	142	146	144				
22	PANCHU	42	F	98	90	99	100	92	102	98	100			140	140	140	136	140	142	140	142			
23	LALITHA	24	F	90	90	94	102	98	96					120	120	124	126	130	124					
24	MATHULAKSHMI	23	F	70	72	80	84	90	90	92				120	120	124	126	130	126	126				
25	CHITHRA	26	F	76	80	88	95	86	94					110	110	118	120	126	124					
26	AMUTHA	36	F	86	82	88	94	96	96	98				130	130	136	140	136	136	134				
27	DANAM	17	F	92	90	102	104	100	98					110	110	116	120	118	118					
28	NIRMALA	34	F	98	100	102	96	98	96	97				130	130	134	140	136	136	130				
29	NIRAIMATHI	42	M	82	84	98	94	88	96	98	88	86		140	140	146	144	142	146	150	146	142		
30	VALLI	32	F	74	76	80	86	90	96	88				130	130	134	136	134	136	134				

CONTROL SHEET 1

SL NO	NAME	AGE	SEX	DBP-PI	DBP-1MIN	DBP-5MIN	DBP-15MIN	DBP-30MIN	DBP-45MIN	DBP-60MIN	DBP-75MIN	DBP-90MIN	DBP-105MIN	FENTANYL REQUIREMENT(MIC)	NO OF DOSES OF ANTI-EMITIC	SCORING OF N &V	POST OP ANALGESIC REQUIREMENT	SEDATION SCORE-1HR	SEDATION SCORE-4HR	SEDATION SCORE-6HR
1	KUPPUSAMY	30	M	80	80	70	70	80	80	80	80	80		140	1	2	2	4	3	3
2	SUBBIAH	34	M	90	80	80	90	90	90	86	86	84		120	NIL	1	3	3	2	2
3	MANIARASU	45	M	90	84	90	90	90	90	90	90	90		120	1	2	2	2	2	2
4	SREENIVASAN	32	M	90	86	90	90	90	90	90	90	90		120	1	2	3	3	2	2
5	BALAKRISHNAN	28	M	90	84	84	90	86	90	86	86			120	1	2	2	2	2	2
6	RAMU	34	M	80	80	90	86	80	90	86	90			120	1	2	2	2	2	2
7	VELLAISAMY	25	M	80	86	80	84	80	80					120	1	2	2	1	2	2
8	ARJUN	18	M	80	80	82	90	80	80	84	86	84		100	1	2	3	3	2	2
9	MARUDUPANDI	34	M	80	84	84	90	86	88	86	90	86		140	1	2	3	4	2	2
10	KARUPPIAH	24	M	70	80	84	84	90	80	80	80			120	1	2	2	2	2	2
11	LOGESHWARI	17	F	70	78	80	80	80	84	82	82			100	1	2	2	2	2	2
12	KASIAMMAL	21	F	80	82	84	90	86	88					100	1	2	2	2	2	2
13	SELVI	18	F	80	82	80	84	84	82	84	90			120	1	2	3	1	2	2
14	PREMA	21	F	80	82	80	84	86	86					100	1	2	2	2	2	2
15	JYOTHI	31	F	80	80	84	86	90	88	82	86	86		120	1	2	3	3	2	2
16	TAMILSELVI	36	F	90	90	86	90	86	90	90				120	2	3	3	2	2	2
17	SUMATHI	19	F	70	74	68	78	80						90	1	2	2	2	2	2
18	SELVAJYOTHI	22	F	90	94	90	94	92	90	92	94			120	1	2	3	3	2	2
19	POONGODI	16	F	70	74	78	80	78	80					80	1	2	2	2	2	2
20	RANI	39	F	90	90	86	90	94	94	96				140	1	2	3	4	2	2
21	VIJAYA	36	F	80	80	86	90	88	90	86				120	1	2	2	2	2	2
22	PANCHU	42	F	80	80	88	84	86	88	90	86			120	1	2	3	2	2	2
23	LALITHA	24	F	80	80	82	84	84	86					120	1	2	2	3	2	2
24	MATHULAKSHMI	23	F	80	80	82	84	84	82	84				120	2	3	3	2	2	2
25	CHITHRA	26	F	70	70	74	78	80	78					120	1	2	2	2	2	2
26	AMUTHA	36	F	80	84	86	90	84	84	80				120	1	2	2	4	3	2
27	DANAM	17	F	70	70	74	80	78	78					90	1	2	2	2	2	2
28	NIRMALA	34	F	80	80	84	90	84	86	84				120	2	3	2	2	2	2
29	NIRAIMATHI	42	M	80	80	84	84	86	90	84	84	84		140	1	2	3	3	2	2
30	VALLI	32	F	80	80	82	84	84	84	84				120	1	2	2	3	2	2

CONTROL SHEET 2